IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 38005-0121

In re patent application of
KONTERMANN, Robert et al.
Serial No. US 09/288,719 Group Art Unit: 1632
Filed: April 09, 1999 Examiner: A. Beckerleg
For: SINGLE-CHAIN MULTIPLE ANTIGEN-BINDING MOLECULE, ITS PREPARATION AND USE

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington D.C. 20231
BOX AF

Sir:

DECLARATION OF DR. ROLAND KONTERMANN

I, Roland Kontermann, do declare as follows:

1. THAT, I am co-inventor of the invention of U.S. patent application serial No. 09/288,719 ("the application"). My curriculum vitae is provided as EXHIBIT (A) hereto.

2. THAT, I received a doctorate degree from the University of Heidelberg, Germany. I have worked in the field of protein engineering since 1992.

3. THAT, I was a research associate at the MRC centre for Protein Engineering in Cambridge, UK from 1993 to 1996.

4. THAT, I have been working in the field of targeting technologies for drug delivery for different diseases (such as, e.g. cancer) since 1993. I have published 14 papers, presented 20 abstracts and held 13 oral presentations at scientific meetings in the field of protein engineering. I published 5 papers and 18 meeting abstracts and oral presentations on engineered proteins for tumor therapy. My list of publications is provided as EXHIBIT (B) hereto.

5. THAT I have reviewed the Office Action of October 10, 2001 in the application. It is my understanding that the Examiner believes that the application fails to provide description for making of single chain binding molecules which bind to both a cell surface target molecule and a vector (page 4). According to the Examiner, the specification fails to guide one of skill to routes and methods of administration of a vector and single chain binding moleucle such that a therapeutic effect on a target cell is observed (page 4)

6. THAT, I conducted and/or supervised experiments which employ the single chain multiple antigen-binding molecule disclosed and claimed in the subject application, used for efficient transfer of vectors into targeted cells. This system provides an effective means for gene therapy.

7. THAT, a person of ordinary skill in the art at the time the invention was filed was able to recognize based on the specification and the examples that the single-chain multiple antigen-binding molecules according to the invention are a versatile tool for in vitro and in vivo transfer of gene constructs into target cells, e.g. single-chain multiple antigen-binding molecules with a gene-construct specific ligand and a target cell specific ligand. The specification, the examples and the technologic knowledge of a skilled worker further more provide sufficient guidance to enable the skilled worker to con-

struct such single-chain multiple antigen-binding molecules according to the invention.

8. THAT, based on Example 1 of the application and the guidance provided in the specification and known teachings in the art, one of ordinary skill in the art could, by conventional means, construct other single chain multiple antigen binding molecules according to the claimed invention, *e.g.,* those which have a specificity for both a plasmid or viral component and a cell surface target molecule: Example 1 shows a single chain multiple antigen binding molecule that is capable of binding CEA and beta-galactosidase, comprising VH1-anti CEA, VL2-anti-beta-galactosidase, VH2-anti-beta-galactosidase, and VL1-anti-CEA (see specification at p. 27, 1. 23 through p. 29,1. 31; see also figure 1). At the time of the invention a skilled artisan would have been able to replace the VH and VL specificities with those for a cell membrane of a target cell and a vector, respectively. Two methods conventionally used to clone VH and VL domains at the time the application was filed are: 1) recruiting established hybridoma-secreting antibodies using the desired specificity as the starting point; and. 2. use antibody phage display libraries to isolate specific antibody fragments *(e.g.,* ScFv, Fab). According to the first method, RNA is isolated from the hybridoma and is reverse transcribed into cDNA, using oligo-DT or random hexamer primers. The VH- and VL-encoding DNA is amplified, *e.g.,* by PCR, using a primer specific for the variable domains, as described by Dubel *et al.*, J. Immunol. Meth. 175:89-95 (1994), and Krebber *et al.*, J. Immunol. Meth. 201:35-55 (1997). According to the second method, such phage display libraries are either generated from immunized *(i.e.,* immune library) or non-immunized *(i.e.,* naiv library) donors, or are generated synthetically by a genetic engineering, as described by Winter *et al.*, Annu. Rev. Immunol. 12:433-55 (1994), and Vaughan *et al.*, Nature Biotechnol. 14:309-14 (1996). Then, specific antibodies are selected using, for example, immobilized purified polypeptides (Nissim *et al.*, J. Immunol. Meth. EMBO J. 13:692-98 (1994)), whole cells (De Kruif *et al.*, J. Mol. Biol. 248:97-105 (1995)), or tissue sections

(Tordsson *et al.*, J. Immunol. Meth. 210:11-23 (1997)). Each method has been successfully applied in various contexts. For example, antibodies have been isolated against DNA, as shown by Young *et al.*, Mol. Immunol. 35:1207-17 (1998). Antibodies have been isolated against viral code proteins as disclosed by Watkins *et al.*, Gene Ther. 4:1004-12 (1996). Also antibodies have been isolated against a large panel of different cell surface antigens such as CEA (Osborne *et al.*, Immunotech. 2:181-96 (1996)) and HMW-MAA (Noronha *et al.*, J. Immunol. 161:296876 (1998)).

As described in the following detailed protocol, the DNA encoding the VH and VL fragments is amplified by PCR with the indicated primers which anneal in the 5' or 3' region, respectively, of the variable regions and which introduce appropriate cloning sites. These fragments are combined into a single-chain multivalent antigen-binding protein by standard molecular techniques generally known to the person skilled in the art. These cloning steps follow protocols published earlier (Kontermann et al., 1997, Immunotechnology 3, 137-144; Kontermann et al., Nature Biotechnology 15, 629-632) and are generally known to the person skilled in the art.

Bispecific single-chain multivalent antigen-binding proteins are generated by converting the first antigen-binding molecule into a bivalent diabody molecule (Holliger et al., 1993, Proc. Natl. Acad. Sci. USA 90, 6444-6448). The variable domains of the second specificity are then inserted into this bivalent diabody construct to obtain a bispecific single-chain multivalent antigen-binding protein. Due to the strong conservation of the 5' and 3' regions of the variable light and heavy chain genes, basically any antibody molecules can be converted to a bispecific single-chain multivalent antigen-binding proteins by means of standard molecular biology techniques (Sambrook et al., 1989, Molecular Cloning, Cold Spring Harbor Laboratory). Bivalent diabodies are generated by substituting the original linker between the VH and VL domain of a single-chain Fv Fragment by a short peptide linker. The standard linker, which is also used in this protocol, is five amino

acids long (with the sequence -GGGGS-). Two configurations are possible: the V_H-V_L configuration, fusing the VL domain to the C-terminal of the V_H domain, and the V_L-V_H configuration, with the V_H domain fused to the C-terminal of the V_L domain. The cloning strategy is based on the introduction of appropriate cloning sites into the V_H and V_L fragments. For the construction of bispecific molecules in the HL configuration, which is described here, a Bst EII site is introduced at the 3' region of the V_H fragment (if not already present) and a Sac I site into the 5' region of the V_L fragment. Bispecific molecules are then generated by combining the V_H and VL fragments from two different antibodies. For this purpose an AscI site is used to combine the DNA fragments. The V_H and VL fragments of an antibody with a second specificity are amplified by PCR to introduce appropriate cloning sites and the middle linker. These fragments are then cloned into a plasmid containing a bivalent diabody in the same configuration. Due to the presence of the middle linker, with a length of 15 amino acids, it is not necessary to introduce a second ribosome binding site and an additional leader sequence.

Restriction site analysis

Restriction sites used for construction in the sequence of the V_H and VL fragments of the antibody fragments to be convert into a bispecific single-chain multivalent antigen-binding proteins are checked for. If additional sites are found partial digests or multiple fragment ligation might have to be used for the generation of antibody fragments. Alternatively, these sites can be deleted by site-directed mutagenesis. It is also possible to introduce other restriction sites suitable for cloning. We have found that most antibody fragments can be cloned as diabodies or single-chain diabodies using the above described restriction sites.

Generation of bivalent diabodies in the VH-VL configuration

Bivalent diabodies are generated by linking a V_H and a V_L domain obtained from the same antibody with a short interdomain linker. An antibody fragment (e.g. a scFv, or Fab fragment) cloned into a bacterial pUC19-derived

expression vector such as pAB1 (Kontermann et al., 1997, Immunotechnology 3, 137-144) can be used as starting material for the generation of a bivalent diabody.

1. Oligonucleotides for amplification of the VH and VL fragments are designed. Approximately 20-30 nucleotides derived from your antibody sequence are used for annealing.
2. Primer LMB3 is used for the VH fragment (annealing in the vector backbone) and a forward primer VHABstFor (introducing a Bst EII site in the 3' region of the VH fragment).
3. Primer LMB2 is used for the VL fragment (annealing in the vector backbone) or fdSeq1 (if the antibody fragment is fused to g3p, i.e. isolated from a phage library) and primer VLABstSacBack annealing in the 5' region of the VL fragment and a Bst EII site, the 5 amino acid linker sequence, and a Sac I site are added to the VL fragment.
4. The VH and the VL fragments are amplified with the respective primers by PCR. Different polymerases including proof-reading ones are used. We routinely perform 25 cycles with an annealing temperature of 50 or 55°C.
5. PCR products are Gel purified. The two fragments should run at approximately 350 bp.
6. The amplified VH fragment is digested with SfiI and Bst EII and the VL fragment with Bst EII and Not I. The reaction conditions supplied by the manufacturer are used. Note: Sfi I needs 50°C reaction temperature and Bst EII 60°C.
7. A bacterial expression vector, such as pAB1, is digested which contains a pelB leader sequence and Sfi I and Not I sites in the multiple cloning site. The digested vector is dephosphorylated with calf intestine alkaline phosphatase.
8. The digested fragments and vector are purified by standard protocols (e.g. phenol/chloroform extraction and ethanol precipitation or using commer-

cially available spin-columns). The amounts are estimated by running aliquots on a 1% agarose gel.

9. The VH and VL fragments are ligated with the vector fragment at 15°C overnight using VH:VL:vector ratios of approximately 2:2:1 in a total volume of 20 µl.
10. 10 µl of the ligation reaction are transformed into TG1 competent cells using standard protocols and plate cells onto TYE, 100 µg/ml ampicillin, 1% glucose plates. Incubate overnight at 37°C.
11. Positive clones are screened by PCR with primers LMB2 and LMB3. To perform the screen, 12-24 single colonies are picked from the plate with sterile toothpicks, dipped into 20 µl of PCR reaction mix (e.g. aliquoted into a 96 well PCR plate) and then streaked it onto a TYE, 100 µg/ml amplicillin, 1% glucose plate (master plate). 30 cycles of PCR are run at an annealing temperature of 50°C and an extention time of 1 min. The PCR products are analyzed on a 1% agarose gel. Positive clones should give a product of approximately 900 bp (VH-VL insert plus flanking vector-derived sequences).
12. Positive clones are analyzed for expression of full-length antibody sequence by immunoblot experiments of bacterial pellets of induced overnight cultures with anti-Myc tag antibody 9E10. Alternatively, the supernatant of an induced 2 ml culture in ELISA is directly checked for antigen binding (protocol 6). The culture is first grown in 2xTY, 100 µg/ml ampicillin, 0.1% glucose until an OD600 of 0.8-1.0 is reached, then 1 mM IPTG are added and incubated at shaking conditions overnight at 30°C.

Generation of bispecific diabodies in the VH-VL configuration

1. The oligonucleotides are designed for amplification of the VH and VL fragments of the second antibody. Approximately 20-30 nucleotides derived from your antibody sequence are used for annealing.
2. Primers VHBAscBack (annealing in the leader sequence and adding an AscI site and the second half of the middle linker sequence) and

VHBSacFor (annealing at the 3' region of the VH fragment and adding a 5 amino acid linker and a SacI site) are used for the VH fragment.

3. Primers VLBBstBack (annealing in the 5' end of the VL fragment and adding a Bst EII site and 5 amino acid linker) and VLBAscFor (annealing in the 3' end of the VL fragment and adding the first half of the middle linker sequence and an Asc I site) are used for the VL fragment.
4. The VH and VL fragments with the respective primers are amplified by PCR and fragments are purified as described in protocol 2.
5. The VH fragment are digested with AscI and Sac I and the VL fragment with Bst EII and Asc I.
6. The bivalent diabody construct in the HL configuration is digested with Bst EII and Sac I.
7. The VLB and VHB fragments is ligated into digested plasmid DNA as described above.
8. The identification of positive clones proceeds as described above.

Primers:

LMB3 5'-CAG GAA ACA GCT ATG ACC-3'

LMB2 5'-GTA AAA CGA CGG CCA GT-3'

fdSeq1 5' GAA TTT TCT GTA TGA GG-3'

Primers for amplification of individual V_H and V_L domains (restriction sites are underlined, dots indicate bases which have to be derived from individual sequences, for annealing these regions should have a length of approximately 20 bases):

V_HABstFor: 5'-CGA GGA GAC GGT GAC CAG ... ...-3' (reverse primer which anneals in the 3' end of V_LA and introducing a *Bst*E II site in the region encoding framework 4).

V_LABstSacBack: 5'-ATC CTG GTC ACC GTC TCC TCG GGC GGT GGC GGA TCC GAT ATC GAG CTC ... ...-3' (anneals in the 5' end of V_LA and introduces a *Bst*E II site, the GGGGS-linker encoding region and a *Sac* I site into V_LA).

V_HBSacFor: 5'-TCG GAG CTC GAT GTC CGA TCC GCC CAA GCC ... ...-3' (reverse primer which anneals in the 3' end of V_HB and introduces DNA encoding a 5 amino acid GGGS linker and a Sac I site).

V_LBBstBack: 5'-GAT CTG GTC ACC GTC TCC TCA GGC GGT GGC GGA TCG ... ...-3' (anneals in the 5' end of V_LB and introduces a *Bst*E II site)..

V_HBAscBack: 5'- TAA GGG CGC GCC TCG GCT GGT AAT ACT AGT ... ...-3' (anneals in the 5' end of V_HB and introduces an *Asc I* site followed by DNA encoding for the second part of middle linker M)

V_LBAscFor: 5'- GCA GGC GCG CCC AGC ATT ACT ATC ACT ACC ... ...-3' (reverse primer which anneals in the 3' end of V_LB and introduces DNA encoding for the first part of middle linker M followed by an *Asc I* site)

9. THAT, the fusogenic peptides listed in EXHIBIT (C) are the same fusogenic peptides disclosed in DE 196 49 645.4, page 10, lines 30-64 and incorporated by reference into the application atpage 10, lines 10 to 14.

10. THAT, the target cell specific ligands listed in EXHIBIT (D) are the same ligands disclosed in DE 196 49 645.4, page 3, line 46 through page 9, line 63 and incorporated by reference into the referring application US 09/288,719, page 10, lines 10-14.

11. THAT, based on the disclosure of the target cell specific ligands disclosed in DE 196 49 645.4, page 3, line 46 through page 9, line 63 and incorporated by reference into the application at page 10, lines 10-14 and further based on the specification of the application and the technical knowledge of one of ordinary skill in the art, such skilled artisan would have been able to identify and construct the VH and/or VL sequences useable as target cell specific ligands. Examples of sequences of such target cell specific ligands are listed in EXHIBIT (E).

12. THAT, gene construct-specific ligands listed in EXHIBIT (F) and incorporated by reference to DE 196 49 645 A1 (listed on page 11, line 55 through page 13, line 40) are the same as the gene construct-specific ligands cited in the application at page 10, lines 10-14..

13. THAT, based on the discloure of the gene construct-specific ligands disclosed in DE 196 49 645.4, page 11, line 55 through page 13, line 40 and incorporated by reference into the application U at page 10, lines 10-14 and further based on the specification of the application and the technical knowledge one of ordinary skill in the art, such skilled artisan would have been able to identify and construct the VH and/or VL sequences useable as gene construct-specific ligands. Examples of sequences of such gene construct-specific ligands are listed in EXHIBIT (G).

14. THAT, a person ordinarily skilled in the art was able to identify and construct the VH and/or VL sequences useable as gene construct-specific ligands based on the specification ofthe application (p. 27, lines 1 to 3: *"Examples of antibodies against viral antigens are: anti-HBV, anti-HCV, anti-HPV, anti-HTLV, anti-coxsackievirus or, anti-hantavirus."),* example 1 and the technical knowledge of the skilled artisan. Such VH or VL sequences are listed in EXHIBIT (G).

15. THAT, a person skilled in the art at the time the invention was filed, based on the information provided in the specification and the knowledge at the time the invention was able to construct single chain multiple antigen binding molecules which bind to both a cell surface target molecule and a vector. Examples of sequences of single chain multiple antigen binding molecules comprising
    - a gene construct-specific ligand selected from the list in EXHIBIT (F) and EXHIBIT (G),
    - a target cell-specific ligand selected from the list in EXHIBIT (D) and EXHIBIT (E)

are described in EXHIBIT (H)

16. THAT, I supervised and/or conducted experiments based on the examples and the specification of the application that prove that based on the information provided in the specification and the knowledge at the time the invention was filed an ordinarily skilled person in the art was able to construct single chain multiple antigen binding molecules which bind to both a cell surface target molecule (human endoglin CD 105) and a vector (adenoviral envelope protein: adenovirus fiber knob domain scDb EDG-Ad) as published by my team Nettelbeck et al., Molec. Ther. 3 (6):882-91 (2001)): The single chain multiple antigen binding molecule described therein is able to bind a vector (adenovirus) and a cell (endothelial cell expressing endoglin CD 105), This further demonstrates the utility of the single chain multiple antigen binding molecules according to the invention for targeting of adenovirus containing a gene construct, preferably a genetherapeutically active gene construct, to cells such as for example cancerous cells.

17. THAT, all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so are made punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing hereon.

Date: 15 Feb. 2002 Signature: R. Kontermann

EXHIBITS

EXHIBIT (A): Curriculum vitae of Dr. R. Kontermann

EXHIBIT (B): List of publications of Dr. R. Kontermann

EXHIBIT (C): Fusogenic peptides cited in DE 196 49 645.4

EXHIBIT (D): Target cell specific ligands cited in DE 196 49 645.4

EXHIBIT (E): Target cell specific ligands

EXHIBIT (F): Gene construct-specific ligands cited in DE 196 49 645.4

EXHIBIT (G): Gene construct-specific ligands

EXHIBIT (H): Sequences of single chain multiple antigen binding molecules

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For: SINGLE-CHAIN MULTIPLE ANTIGEN-BINDING MOLECULE, ITS PREPARATION AND USE

EXHIBIT A

Curriculum vitae

Roland E. Kontermann, Ph.D.
- Molecular Biologist -

Address	Lerchengasse 5, 35085 Ebsdorfergrund, Germany
Date of birth	6 February 1961
Place of birth	Urbach (Germany)
Nationality	German
Marital status	married

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since Jan. 2001	Head of the Biotechnology Department of vectron therapeutics AG
2001	Habilitation (venia legendi) in Molecular Biology
March 1996 - Dec. 2000	research associate at the Institute of Molecular Biology and Tumor Research of the University of Marburg

Oct. 1993 - Feb. 1996	research associate at the MRC Centre for Protein Engineering (Cambridge, England) in the laboratory of Dr. Greg Winter
July 1992 - Sept. 1993	research associate at the Institute of Molecular Genetics of the University of Heidelberg
July 1992	Ph.D. in molecular biology
Jan. 1989 - July 1992	Ph.D. thesis at the Institute of Molecular Genetics of the University of Heidelberg
Aug. 1987 - Nov. 1988	civil service at the Institute of Immunology of the University of Heidelberg
Sept. 1987	Diploma in biology
1986 - 1987	Diploma thesis at the Institute of Molecular Genetics of the University of Heidelberg
1980 - 1987	studied biology at the University of Hohenheim subjects: genetics, zoology, biochemistry, microbiology
1977 - 1980	grammar school of economy
1971 - 1977	intermediate school
1967 - 1971	elementary school

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EXHIBIT B

List of Publications of Roland E. Kontermann

A. Scientific publications

1. **Kontermann, R.**, Sitzler, S., Seifarth, W., Petersen, G. & Bautz, E.K.F. (1989)

   Primary structure and functional aspects of the gene coding for the second-largest subunit of RNA polymerase III of *Drosophila melanogaster.*

   Mol. Gen. Genet. **219**, 373-380.

2. **Kontermann, R.** & Rauterberg, E.W. (1989)

   N-deglycosylation of human complement component C9 reduces its hemolytic activity.

   Mol. Immunol. **26**, 1125-1132.

3. **Kontermann, R.**, Deppisch, R. & Rauterberg, E.W. (1990)

   Several epitopes of human complement C9 are involved in interaction with the C5b-8 complex and other C9 molecules.
   Eur. J. Immunol. **20**, 623-628.

4. Seifarth, W., Petersen, G., **Kontermann, R.**, Riva, M., Huet, J. & Bautz, E.K.F. (1991)

Identification of the genes for the second-largest subunits of RNA polymerase I and III of *Drosophila melanogaster.*

Mol. Gen. Genet. **228**, 424-432.

5. Ng, S.W., Wiedemann, M., **Kontermann, R.** & Petersen, G. (1992)

Molecular characterization of a putative peroxidase gene of *Drosophila melanogaster.*

Biochim. Biophys. Acta **1171**, 224-228.

6. **Kontermann, R.** & Bautz, E.K.F. (1992)

Similarity between subunit 8 of yeast RNA polymerase II (RPB8) and the second-largest subunits of eukaryotic RNA polymerases.
Nucleic Acids Res. **20**, 5321.

7. Liu, Z., **Kontermann, R.E.**, Schulze, R.A., Petersen, G. and Bautz, E.K.F. (1993)

RPII15 codes for the M_r 15 000 subunit 9 of *Drosophila melanogaster* RNA polymerase II.

FEBS Lett. **335**, 73-75.

8. **Kontermann, R.E.**, Kobor, M. & Bautz, E.K.F. (1993)

Identification of a nucleic acid-binding region within the largest subunit of *Drosophila melanogaster* RNA polymerase II.

Protein Sci. **2**, 223-230.

9. Schulze, R.A., **Kontermann, R.E.**, Queitsch, I., Dübel, S. & Bautz, E.K.F. (1994)

Thiophilic adsorption chromatography of recombinant single-chain antibody fragments.
Anal. Biochem. **220**, 212-214.

10. **Kontermann, R.E.** & Bautz, E.K.F. (1994)

Nucleic acid-binding regions of the second-largest subunit of *Drosophila* RNA polymerase II identified by Southwestern blotting.

FEBS Lett. **334**, 166-170.

11. Griffiths, A.D., Williams, S.C., Hartley, O., Tomlinson, I.M., Waterhouse, P., Crosby, W.L., **Kontermann, R.E.**, Jones, P.T., Low, N.M., Allison, J., Prospero, T.D., Hoogenboom, H.R., Nissim, A., Cox, J.P.L., Harrison, J.L., Zaccolo, M., Gherardi, E. & Winter, G. (1994)

Isolation of high affinity human antibodies directly from large synthetic repertoires.

EMBO J. **13,** 3245-3260.

12. Kipriyanov, S.M., Dübel, S., Breitling, F., **Kontermann, R.E.** & Little, M. (1994)

Recombinant single-chain Fv fragments carrying C-terminal cysteine residues: production of bivalent and biotinylated miniantibodies.
Mol. Immunol. **31**, 1047-1058.

13. Dübel, S., Breitling, F., **Kontermann, R.**, Schmidt, T., Skerra, A. & Little, M. (1995)

Bifunctional and multimeric complexes of streptavidin fused to single chain antibodies (scFv).
J. Immunol. Meth. **178,** 201-209.

14. Kipriyanov, S.M., Dübel, S., Breitling, F., **Kontermann, R.E.**, Heymann, S. & Little, M. (1995)

Bacterial expression and refolding of single-chain Fv fragments with C-terminal cysteines.
Cell Biophysics **26**, 187-204.

15. **Kontermann, R.E.**, Liu, Z., Schulze, R.A., Sommer, K.A., Queitsch, I., Dübel, S., Kipriyanov, S.M., Breitling, F. & Bautz, E.K.F. (1995)

Characterization of the epitope recognized by a monoclonal antibody directed against the largest subunit of *Drosophila* RNA polymerase II.

Biol. Chem. **376**, 473-481.

16. Fisch, I., **Kontermann, R.E.**, Finnern, R., Hartley, O., Soler-Gonzales, A., Griffiths, A.D. & Winter, G. (1996)

A strategy of exon shuffling for making large peptide repertoires displayed on filamentous bacteriophage.
Proc. Natl. Acad. Sci. USA **93**, 7761-7766.

17. **Kontermann, R.E.**, Martineau, P., Cummings, C.E., Karpas, A., Allen, D., Derbyshire, E. & Winter, G. (1997)

Enzyme immunoassays using bispecific diabodies.
Immunotechnology **3**, 137-144.

18. **Kontermann, R.E.**, Wing, M.G. & Winter, G. (1997)

Complement recruitment using bispecific diabodies.

Nature Biotechnology **15**, 629-631.

19. Heidtmann, H.-H. & **Kontermann, R.E.** (1998)

Cloning and recombinant expression of mouse coagulation factor X.
Thromb. Res. **92**, 33-41.

20. Brüsselbach, S., Korn, T., Völkel, T., Müller, R. & **Kontermann, R.E.** (1999)

Enzyme recruitment and tumor cell killing in vitro by a secreted bispecific single-chain diabody.
Tumor Targeting **4**, 115-123.

21. **Kontermann, R.E.** & Müller, R. (1999)

Intracellular and cell surface displayed single-chain diabodies.

J. Immunol. Meth. **226**, 179-188.

22. Alt, M., Müller, R. & **Kontermann, R.E.** (1999)

Novel tetravalent and bispecific IgG-like antibody molecules combining single-chain diabodies with the immunoglobulin □1 Fc or CH3 region.
FEBS Lett. **454**, 90-94

23. Heidtmann, H.-H., Nettelbeck, D.M., Mingels, A., Jäger, R., Welker, H.-G. & **Kontermann, R.E.** (1999)

Generation of angiostatin-like fragments from plasminogen by prostate-specific antigen.
Br. J. Cancer **81**, 1269-1273.

24. Nettelbeck, D.M., Miller, D.W., Jérôme, V., Zuzarte, M., Watkins, S.J., Hawkins, R.E., Müller, R. & **Kontermann, R.E.** (2001)

Targeting of adenovirus to endothelial cells by a bispecific single-chain diabody directed against the adenovirus fiber knob domain and human endoglin (CD105).

Mol. Ther. **3**, 882-891.

25. Völkel, T., Korn, T., Bach, M., Müller, R. & **Kontermann, R.E.** (2001)

Optimised linker sequences for the expression of monomeric and dimeric bispecific single-chain diabodies

Protein Eng. **14**, 815-823.

B. Reviews

1. **Kontermann, R.E.** (2000)
   Recombinant antibody fragments for cancer therapy.
   Mod. Asp. Immunobiol. **1**, 88-91.

C. Books and book chapters

1. **Kontermann, R.E. &** Dübel, S. (Hrsg.) (2001)
   Antibody engineering, a lab manual.
   Springer-Verlag Heidelberg.

2. Dübel, S. & **Kontermann, R.E.** (2001)
   Recombinant antibodies
   In: Antibody engineering, a lab manual. Kontermann, R.E. & Dübel, S. (Hrsg.)
   Springer-Verlag Heidelberg. pp 3-18.

3. **Kontermann, R.E.** (2001)
   Immunotube selections.
   In: Antibody engineering, a lab manual. Kontermann, R.E. & Dübel, S. (Hrsg.)
   Springer-Verlag Heidelberg. pp 137-148.

4. Winter, C.H. & **Kontermann, R.E.** (2001)
   Epitope mapping with gene-fragment libraries.
   In: Antibody engineering, a lab manual. Kontermann, R.E. & Dübel, S. (Hrsg.)
   Springer-Verlag Heidelberg. pp 473-490.

5. Korn, T., Völkel, T. & **Kontermann, R.E.** (2001)
   Bivalent and bispecific diabodies and single-chain diabodies.
   In: Antibody engineering, a lab manual. Kontermann, R.E. & Dübel, S. (Hrsg.)
   Springer-Verlag Heidelberg. pp 619-636.

6. **Kontermann, R.E.**, Korn, T. & Jérôme, V. (2002)
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   5. Frühjahrestagung der Gesellschaft für Immunologie, Freiburg.

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8. Ng, S.-W., **Kontermann, R.**, Petersen, G. & Bautz, E.K.F. (1990)

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Molecular analysis of cDNA and genomic sequences encoding a putative peroxidase gene of *Drosophila melanogaster.*
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10. Frühjahrestagung der Gesellschaft für Immunologie, Heidelberg.

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Complement recruitment using bispecific diabodies.

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15. **Kontermann, R.E.,** Wing, M.G. & Winter, G. (1996)

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18. Montigiani, S., Müller, R. & **Kontermann, R.E.** (1999)

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19. Nettelbeck, D.M., Watkins, S.J., Hawkins, R.E., Müller, R. & **Kontermann, R.E.** (1999)

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Bispecific single-chain diabodies.

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25. **Kontermann, R.E.**, Korn, T., Völkel, T., Alt, M., Müller, R. & Brüsselbach, S. (1999)

Bispecific single-chain diabodies secreted from mammalian producer cells for the recruitment of effector mechanisms to tumour cells.

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1st International Symposium on Genetic Anticancer Agents. Amsterdam, Niederlande.

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Bispecific single-chain diabodies.

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Bispecific single-chain diabodies for the retargeting of vectors and effectors.
Cold Spring Harbor Laboratory Meeting on 'Vector Targeting Strategies for Therapeutic Gene Delivery'.

E. Oral presentations

1. Isolation of high affinity antibody fragments directly from large antibody repertoires.

   RNA Polymerase Symposium, Akademie der Wissenschaften, Heidelberg (Oktober 1994)

2. Isolation of high affinity antibody fragments directly from large antibody repertoires.

   MPI für Immunbiologie, Freiburg, i.B. (Februar 1995)

3. Isolation of high affinity antibody fragments directly from large antibody repertoires.

   Klinik für Tumorbiologie, Freiburg, i.B. (Februar 1995)

4. Bispezifische Diabodies für die Rekrutierung von Effektorfunktionen.

   Behringwerke Marburg (1996)

5. New developments in filamentous phage display technology – isolation of high affinity antibody fragments and peptides.

   36. Biochemie-Kolloqium des Instituts für Biochemie der Friedrich-Schiller-Universität, Jena (Juni 1996)

6. Rekombinante Antikörperfragmente in Diagnostik und Therapie.

   Seminarreihe der Abteilung Hämatologie und Onkologie des Zentrums für Innere Medizin der Philipps-Universtät, Marburg (1997)

7. „Naïve" Antikörperbibliotheken.

   18. Sitzung des DECHEMA-Arbeitsausschusses „Grundlagen der Stoffproduktion", Frankfurt/Main (September 1998)

8. Bispezifische Antikörperfragmente für die Tumortherapie.

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9. Bispecific single-chain diabodies: Developments for immunotherapy and gene therapy of cancer

Seminarreihe des Instituts für Biologie I, Rheinisch-Westfälische Technische Hochschule Aachen (April 2000)

10. Targeting of vectors and effectors with recombinant bispecific antibodies.

Gene therapy seminar series am Gene Therapy Center at the University of Alabama at Birmingham (März 2001).

11. Vector and effector targeting with bispecific recombinant antibodies.

Cold Spring Harbor Laboratory Meeting on 'Vector Targeting Strategies for Therapeutic Gene Delivery' (März 2001).

12. Rekombinante bispezifische Antikörper für die Behandlung von Krebs.

Immunologisches Kolloquim, Institut für Immunologie, Universität Kiel (Juni 2001).

13. Einsatz rekombinanter Antikörperfragmente in der Medizin.

Journal Club, Aventis Behring, Marburg (September 2001).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 38005-0121

In re patent application of
Robert KONTERMANN et al.
Serial No. US 09/288,719 Group Art Unit: 1632
Filed: April 09, 1999 Examiner: A. Beckerleg
For: SINGLE-CHAIN MULTIPLE ANTIGEN-BINDING MOLECULE, ITS PREPARATION AND USE

EXHIBIT C

Fusogenic peptides cited in
DE 196 49 645 A1

The fusogenic peptides disclosed in DE 196 49 645.4 and listed on page 10, lines 30-64 and comprise for example:

(1) peptide containing the peptide GLFEALLELLESLWELLLEA (Gottschalk *et al.,* Gene Ther. 3, 448 (1996));

(2) peptide containing the peptide AALAEA[LAEA]$_4$LAAAGC (Acm) (Wang *et al.,* Technol. Advances in Vector Syst. For Gene Ther., May 6-7, 1996, Coronado, IBC Conference);

(3) peptide containing the peptide FAGV-VLAGAALGVAAAAQI of the fusion protein of measles-virus (Yeagle *et al.,* Biochem. Bioühys. Acta 1065, 49 (1991));

(4) peptide containing the peptide GLFGAIAGFIEGGWWGMIDG of the HA2 proteins of Influenza A (Lüneberg *et al.,* J. Biol. Chem. 270, 27606 (1995));

(5) peptide containing the peptide GLFGAIAGFIENGWEGMIDG GLFGAIAGFIENGWEGMIDG (Burger *et al.,* Biochem. 30, 11173 (1991)) or the peptide GLFGAIAGFIE; ALFGAIAGFIE;

LFLGAIAGFIE; LLLGAIAGFIE; LILGAIAGFIE; GIFGAIAGFIE; GLLGAIAGFIE; GLFAAIAGFIE; GLFEAIAGFIE; GLFGAMAGFIE; GLFGAIAGLIE or the peptide GLFGAIAGFIV (Steinhauer *et al.*, J. Virol. 69, 6643 (1995));

(6) the peptide GLFEAIAEFIEGGWEGLIEG; and

(7) the peptide GLLEALAELLEGGWEGLLEG (Ishiguro *et al.*, Biochem. 32, 9792 (1993)).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 38005-0121

In re patent application of
Robert KONTERMANN et al.
Serial No. US 09/288,719 Group Art Unit: 1632
Filed: April 09, 1999 Examiner: A. Beckerleg
For: SINGLE-CHAIN MULTIPLE ANTIGEN-BINDING MOLECULE, ITS PREPARATION AND USE

EXHIBIT D

Target cell specific ligands cited in DE 196 49 645 A1

The target cell specific ligands disclosed in DE 196 49 645.4 and listed on page 3, line 46 through page 9, line 63 comprise inter alia:

(1) antibody fragments directed against membrane structures of endothelial cells such as, for example, Burrows *et al.* (Pharmac. Ther. 64, 155 (1994), Hughes *et al.* (Cancer Res. 49, 6214 (1989) and Murayama *et al.* (PNAS-USA 87, 5744 (1990)) specially antibodies against VEGF-receptors. (disclosed in DE 196 49 645 Al, p. 5, lines 19-22);

(2) antibodies or antibody fragments directed against membrane structures of immune cells, such as described in Powelson *et al.*, Biotech. Adv. 11, 725 (1993) or antibodies or antibodyfragments that bind with their antigen binding part the FC-γ, FC-ε or FC-μ (Rojanasakul et al. Pharm. Res. 11, 1731 (1994), (disclosed in DE 196 49 645 Al, p. 5, lines 50-61);

(3) antibodies or antibody fragments directed against membrane structures of muscle cells, such as the antibody 10F3, antibody against actin, antibody against angiotensin II receptors or antibodies against receptors of growth factors (disclosed in DE 196 49 645 Al, p. 6, lines 48-56);

(4) antibodies or antibody fragments directed against membrane structures of tumor cells, such antibodies are described in Sedlacek *et al.,* Contrib. to Oncol. 32, Karger Publisher, Munich (1998) and Contrib. to Oncol. 43, Karger Publisher, Munich (1992) (disclosed in DE 196 49 645 Al, page 9, lines 50-54).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 38005-0121

In re patent application of

Robert KONTERMANN et al.

Serial No. US 09/288,719 Group Art Unit: 1632

Filed: April 09, 1999 Examiner: A. Beckerleg

For: SINGLE-CHAIN MULTIPLE ANTIGEN-BINDING MOLECULE, ITS PREPARATION AND USE

EXHIBIT E

Gene construct-specific ligands

Such ligands comprise:

1. Anti-Fc-γ receptor I (specific ligand for NK cells, macrophages, etc.) Tempest, P.R., Submitted to the National Center for Biological Resources, (NCBI, accessible through http://www.ncbi.nlm.nih.gov/) 30-JUN-1995,

VH-Version: Accession number: Z50001.1 GI:895695

1 caggtccaac tgcaggagag cggtccaggt cttgtgagac ctagccagac cctgagcctg

61 acctgcaccg tgtctggctt cattttcagc gacaattaca tgtattgggt gagacagcca

121 cctggacgag gtcttgagtg gattggaacc attagtgatg gtggtagtta cacctactat

181 cctgacagtg tgaaggggag agtgacaatg ctgagagaca ccagcaagaa ccagttcagc

241 ctgagactca gcagcgtgac agccgccgac accgcggtct attattgtgc aagaggctac

301 tataggtacg aggggggctat ggactactgg ggccaagggt ccttggtcac cgtctcctca

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1/1                                                 31/11
61/21                                               91/31

cag gtc caa ctg cag gag agc ggt cca ggt ctt gtg aga cct agc
cag acc ctg agc ctg acc tgc acc gtg tct ggc ttc att ttc agc
gac aat tac atg tat tgg gtg aga cag cca

Q   V   Q   L   Q   E   S   G   P   G   L   V   R   P   S   Q
T   L   S   L   T   C   T   V   S   G   F   I   F   S   D   N
Y   M   Y   W   V   R   Q   P

121/41                                              151/51
181/61                                              211/71

cct gga cga ggt ctt gag tgg att gga acc att agt gat ggt ggt
agt tac acc tac tat cct gac agt gtg aag ggg aga gtg aca atg
ctg aga gac acc agc aag aac cag ttc agc

P   G   R   G   L   E   W   I   G   T   I   S   D   G   G   S
Y   T   Y   Y   P   D   S   V   K   G   R   V   T   M   L   R
D   T   S   K   N   Q   F   S

241/81                                              271/91
301/101                                             331/111

ctg aga ctc agc agc gtg aca gcc gcc gac acc gcg gtc tat tat
tgt gca aga ggc tac tat agg tac gag ggg gct atg gac tac tgg
ggc caa ggg tcc ttg gtc acc gtc tcc tca

L   R   L   S   S   V   T   A   A   D   T   A   V   Y   Y   C
A   R   G   Y   Y   R   Y   E   G   A   M   D   Y   W   G   Q
G   S   L   V   T   V   S   S
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VL-Version: Accession number: Z50002.1 GI:895696

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1 gacatccagc tgacccagag cccaagcagc ctgagcgcca gcgtgggtga ca-
gagtgacc

61 atcacctgta agtccagtca aagtgtttta tacagttcaa atcagaagaa
ctacttggcc

121 tggtaccagc agaagccagg taaggctcca aagctgctga tctactgggc
atccactagg

181 gaatctggtg tgccaagcag attcagcggt agcggtagcg gtaccgactt
caccttcacc

241 atcagcagcc tccagccaga ggacatcgcc acctactact gccatcaata
cctctcctcg

301 tggacgttcg gccaagggac caaggtggaa atcaaa
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1/1                                                 31/11
61/21                                               91/31
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```
gac atc cag ctg acc cag agc cca agc agc ctg agc gcc agc gtg
ggt gac aga gtg acc atc acc tgt aag tcc agt caa agt gtt tta
tac agt tca aat cag aag aac tac ttg gcc

D   I   Q   L   T   Q   S   P   S   S   L   S   A   S   V   G
D   R   V   T   I   T   C   K   S   S   Q   S   V   L   Y   S
S   N   Q   K   N   Y   L   A

121/41                                  151/51
181/61                                  211/71

tgg tac cag cag aag cca ggt aag gct cca aag ctg ctg atc tac
tgg gca tcc act agg gaa tct ggt gtg cca agc aga ttc agc ggt
agc ggt agc ggt acc gac ttc acc ttc acc

W   Y   Q   Q   K   P   G   K   A   P   K   L   L   I   Y   W
A   S   T   R   E   S   G   V   P   S   R   F   S   G   S   G
S   G   T   D   F   T   F   T

241/81                                  271/91
301/101                                 331/111

atc agc agc ctc cag cca gag gac atc gcc acc tac tac tgc cat
caa tac ctc tcc tcg tgg acg ttc ggc caa ggg acc aag gtg gaa
atc aaa

I   S   S   L   Q   P   E   D   I   A   T   Y   Y   C   H   Q
Y   L   S   S   W   T   F   G   Q   G   T   K   V   E   I   K
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2. anti-CD3 (specific ligand for cytotoxic T lymphocytes) Gilliland,L.K., et al. Tissue Antigens 47 (1), 1-20 (1996) Sequence dadabase: National Center for Biological Resources, (NCBI, accessible through http://www.ncbi.nlm.nih.gov/)

VH-Version Accession number AF000359.1 GI:2522357

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58 cag

61 gtcaagctgc agcagtccgg ttctgaacta gggaaacctg gggcctcagt
gaaactgtcc

121 tgcaagactt caggctacat attcacagat cactatattt cttgggtgaa aca-
gaagcct

181 ggagaaagcc tgcagtggat aggaaatgtt tatggtggaa atggtggtac aagcta-
caat

241 caaaaattcc agggcaaggc cacactgact gtagataaaa tctctagcac agccta-
catg

301 gaactcagca gcctgacatc tgaggattct gccatctatt actgtgcaag
aaggccggta

361 gcgacgggcc atgctatgga ctactggggt caggggatcc aagttaccgt ctcctca
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1/1                                                 31/11
61/21                                               91/31

cag gtc aag ctg cag cag tcc ggt tct gaa cta ggg aaa cct ggg gcc
tca gtg aaa ctg tcc tgc aag act tca ggc tac ata ttc aca gat cac
tat att tct tgg gtg aaa cag aag

Q   V   K   L   Q   Q   S   G   S   E   L   G   K   P   G   A   S
V   K   L   S   C   K   T   S   G   Y   I   F   T   D   H   Y   I
S   W   V   K   Q   K

121/41                                              151/51
181/61                                              211/71

cct gga gaa agc ctg cag tgg ata gga aat gtt tat ggt gga aat ggt
ggt aca agc tac aat caa aaa ttc cag ggc aag gcc aca ctg act gta
gat aaa atc tct agc aca gcc tac

P   G   E   S   L   Q   W   I   G   N   V   Y   G   G   N   G   G
T   S   Y   N   Q   K   F   Q   G   K   A   T   L   T   V   D   K
I   S   S   T   A   Y

241/81                                              271/91
301/101                                             331/111

atg gaa ctc agc agc ctg aca tct gag gat tct gcc atc tat tac tgt
gca aga agg ccg gta gcg acg ggc cat gct atg gac tac tgg ggt cag
ggg atc caa gtt acc gtc tcc tca

M   E   L   S   S   L   T   S   E   D   S   A   I   Y   Y   C   A
R   R   P   V   A   T   G   H   A   M   D   Y   W   G   Q   G   I
Q   V   T   V   S   S
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VL-Version Accession number AF000358.1 GI:2522355

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61 gacatagtgc tgactcagac tccagccact ctgtctctaa ttcctggaga aagagt-
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121 atgacctgta agaccagtca gaatattggc acaatcttac actggtatca
ccaaaaacca

181 aaggaggctc caagggctct catcaagtat gcttcgcagt ccattcctgg
gatcccctcc

241 agattcagtg gcagtggttc ggaaacagat ttcactctca gcatcaataa
cctggagcct

301 gatgatatcg gaatttatta ctgtcaacaa agtagaagct ggcctgtcac
gttcggtcct

361 ggcaccaagc tggagataaa a
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1/1                                                 31/11
61/21                                               91/31
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```
gac ata gtg ctg act cag act cca gcc act ctg tct cta att cct gga
gaa aga gtc aca atg acc tgt aag acc agt cag aat att ggc aca atc
tta cac tgg tat cac caa aaa cca

D   I   V   L   T   Q   T   P   A   T   L   S   L   I   P   G   E
R   V   T   M   T   C   K   T   S   Q   N   I   G   T   I   L   H
W   Y   H   Q   K   P

121/41                                      151/51
181/61                                      211/71

aag gag gct cca agg gct ctc atc aag tat gct tcg cag tcc att cct
ggg atc ccc tcc aga ttc agt ggc agt ggt tcg gaa aca gat ttc act
ctc agc atc aat aac ctg gag cct

K   E   A   P   R   A   L   I   K   Y   A   S   Q   S   I   P   G
I   P   S   R   F   S   G   S   G   S   E   T   D   F   T   L   S
I   N   N   L   E   P

241/81                                      271/91
301/101

gat gat atc gga att tat tac tgt caa caa agt aga agc tgg cct gtc
acg ttc ggt cct ggc acc aag ctg gag ata aaa

D   D   I   G   I   Y   Y   C   Q   Q   S   R   S   W   P   V   T
F   G   P   G   T   K   L   E   I   K
```

Antibody against ovarina, cerix, breast and colon carcinoma (ligands specific for membrane structures of tumor cells) Chen,P.F., et al., Hum. Antibodies Hybridomas 5 (3-4), 131-142 (1994), Sequence dadabase: National Center for Biological Resources, (NCBI, accessible through http://www.ncbi.nlm.nih.gov/)

VH-Version Accession Number S77598.1 GI:998388

```
58 cag

61 gtgcagctgg tgcagtctgg ggctgaggtg aagaagcctg gggcctcagt
gaaggtttcc

121 tgcaaggcat ctggatacac cttcaccagc tactatatgc actgggtcga
acaggcccct

181 ggacaagggc ttgagtggat gggaataatc aaccctagtg gtggtagcac
aagctacgca

241 cagaagttcc agggcagagt caccatgacc agggacacgt ccacgagcac agtcta-
catg

301 gagctgagca gcctgagatc tgaggacacg gccgtgtatt actgtgctag agag-
gatggg

361 cctacagcta tggccacaag ggccgaccta acgacaacat actactacta
ctacggtatg

421 gacgtctggg gccaagggac cacggtcacc gtctcctca
```

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1/1                                                 31/11
61/21                                               91/31

cag gtg cag ctg gtg cag tct ggg gct gag gtg aag aag cct ggg gcc
tca gtg aag gtt tcc tgc aag gca tct gga tac acc ttc acc agc tac
tat atg cac tgg gtc gaa cag gcc                                .

Q   V   Q   L   V   Q   S   G   A   E   V   K   K   P   G   A   S
V   K   V   S   C   K   A   S   G   Y   T   F   T   S   Y   Y   M
H   W   V   E   Q   A

121/41                                              151/51
181/61                                              211/71

cct gga caa ggg ctt gag tgg atg gga ata atc aac cct agt ggt ggt
agc aca agc tac gca cag aag ttc cag ggc aga gtc acc atg acc agg
gac acg tcc acg agc aca gtc tac

P   G   Q   G   L   E   W   M   G   I   I   N   P   S   G   G   S
T   S   Y   A   Q   K   F   Q   G   R   V   T   M   T   R   D   T
S   T   S   T   V   Y

241/81                                              271/91
301/101                                             331/111

atg gag ctg agc agc ctg aga tct gag gac acg gcc gtg tat tac tgt
gct aga gag gat ggg cct aca gct atg gcc aca agg gcc gac cta acg
aca aca tac tac tac tac tac ggt

M   E   L   S   S   L   R   S   E   D   T   A   V   Y   Y   C   A
R   E   D   G   P   T   A   M   A   T   R   A   D   L   T   T   T
Y   Y   Y   Y   Y   G

361/121                                             391/131

atg gac gtc tgg ggc caa ggg acc acg gtc acc gtc tcc tca

M   D   V   W   G   Q   G   T   T   V   T   V   S   S
```

VL-VERSION Accession Number S77599.1 GI: 998390

```
61 gagctgacac agccaccctc ggtgtcagtg tccctaggac agatggccag gat-
cacctgc

121 tctggagaag cattgccaaa aaaatatgct tattggtacc agcagaagcc
aggccagttc

181 cctgtgctgg tgatatataa agacagcgag agggcctcag ggatccctga
gcgattctct

241 ggctccagct cagggacaat agtcacattg accatcagtg gagtccaggc agaa-
gacgag

301 gctgactatt actgtctatc agcagacagc agtggtactt atggcgggtg
gttcggcgga
```

```
361 gggaccaagc tgaccgtcct a


1/1                                             31/11
61/21                                           91/31

gag ctg aca cag cca ccc tcg gtg tca gtg tcc cta gga cag atg gcc
agg atc acc tgc tct gga gaa gca ttg cca aaa aaa tat gct tat tgg
tac cag cag aag cca ggc cag ttc

E   L   T   Q   P   P   S   V   S   V   S   L   G   Q   M   A   R
I   T   C   S   G   E   A   L   P   K   K   Y   A   Y   W   Y   Q
Q   K   P   G   Q   F

121/41                                          151/51
181/61                                          211/71

cct gtg ctg gtg ata tat aaa gac agc gag agg gcc tca ggg atc cct
gag cga ttc tct ggc tcc agc tca ggg aca ata gtc aca ttg acc atc
agt gga gtc cag gca gaa gac gag

P   V   L   V   I   Y   K   D   S   E   R   A   S   G   I   P   E
R   F   S   G   S   S   S   G   T   I   V   T   L   T   I   S   G
V   Q   A   E   D   E

241/81                                          271/91
301/101

gct gac tat tac tgt cta tca gca gac agc agt ggt act tat ggc ggg
tgg ttc ggc gga ggg acc aag ctg acc gtc cta

A   D   Y   Y   C   L   S   A   D   S   S   G   T   Y   G   G   W
            F   G   G   G   T   K   L   T   V   L
```

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 38005-0121

In re patent application of
Robert KONTERMANN et al.
Serial No. US 09/288,719 Group Art Unit: 1632
Filed: April 09, 1999 Examiner: A. Beckerleg
For: SINGLE-CHAIN MULTIPLE ANTIGEN-BINDING MOLECULE, ITS PREPARATION AND USE

EXHIBIT F

Gene construct-specific ligands cited in DE 196 49 645 A1

The gene construct-specific ligands disclosed in DE 196 49 645.4 and listed on page 11, line 55 through page 13, line 40 comprise inter alia:

(1) antibodies directed against epitopes newly introduced into DNA such as antibodies directed against methylated DNA, antibodies against O^6-ethyl deoxyguanosin, antibodies against N^5-methyl-N5-formyl-2,5,6,-triamino-4-hydroxypyrimidine, antibodies against N7-ethyl guanine, antibodies against 0^6-methyl-2'-deoxyguanosine, antibodies against 0^6-ethyl-2'-deoxyguanosine, antibodies against 0^6-N-butyl-2'- deoxyguanosine, antibodies against 0^6-isopropyl-2'-deoxyguanosine, antibodies against 0^4-methyl-2'-deoxyguanosine or antibodies against 0^4-ethyl-2'-deoxyguanosine, antibodies against methylated DNA, especially against N^6-methylated adenin.

(2) antibodies directed against envelope proteins or viruses such as for example

- murine leukemia virus, the antibody being preferably directed against envelope proteins gp70 and p15,
- HIV,
- herpes simplex virus, the antibody being preferably directed against glycoprotein B, glycoprotein H, glycoprotein L,
- cytomegalovirus, the antibody being preferably directed against glycoprotein B (gpB),
- adanoassociated virus,
- minute virus of mice,
- antibodies against adanoassociated virus, the antibody being preferably directed against Cap- and Rep-proteins,
- cytomegalovirus, the antibody being preferably directed against glycoprotein B (gpB),

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 38005-0121

In re patent application of

Robert KONTERMANN et al.

Serial No. US 09/288,719 Group Art Unit: 1632

Filed: April 09, 1999 Examiner: A. Beckerleg

For: SINGLE-CHAIN MULTIPLE ANTIGEN-BINDING MOLECULE, ITS PREPARATION AND USE

EXHIBIT G

Gene construct-specific ligands

Such antibodies against DNA comprise inter alia:

Anti-DNA antibodies (ligands specific for DNA) Jang,Y.J. et al., Mol. Immunol. 33 (2), 197-210 (1996) Sequence dadabase: National Center for Biological Resources, (NCBI, accessible through http://www.ncbi.nlm.nih.gov/) Accession number 96215469

VH-Version Accession number U23046.1 GI:736417

```
1 caggtccaac tacagcagcc tggtgctgag cttgtgaagc ctggggcctc agt-
gaagctg

61 tcctgcaagg cttctggcta cactttcacc aggttctgga taaactgggt gaggca-
gagg

121 cctggacaag gccttgagtg gattggaaat atttatcctg gtagtagtag tat-
taactac

181 aatgagaagt tcaagaacaa ggccacactg actgtagaca catcctccag ca-
cagcctac

241 atgcagctca gcagcctgac atctgacgac tctgcggtct attattgtgc aa-
gacggcgg

301 tataggtcct cctatgctat ggactactgg ggtcaaggaa cctcagtcac
cgtctcctca
```

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1/1                                                 31/11
61/21                                               91/31

cag gtc caa cta cag cag cct ggt gct gag ctt gtg aag cct ggg gcc
tca gtg aag ctg tcc tgc aag gct tct ggc tac act ttc acc agg ttc
tgg ata aac tgg gtg agg cag agg

Q   V   Q   L   Q   Q   P   G   A   E   L   V   K   P   G   A   S
V   K   L   S   C   K   A   S   G   Y   T   F   T   R   F   W   I
N   W   V   R   Q   R

121/41                                              151/51
181/61                                              211/71

cct gga caa ggc ctt gag tgg att gga aat att tat cct ggt agt agt
agt att aac tac aat gag aag ttc aag aac aag gcc aca ctg act gta
gac aca tcc tcc agc aca gcc tac

P   G   Q   G   L   E   W   I   G   N   I   Y   P   G   S   S   S
I   N   Y   N   E   K   F   K   N   K   A   T   L   T   V   D   T
S   S   S   T   A   Y

241/81                                              271/91
301/101                                             331/111

atg cag ctc agc agc ctg aca tct gac gac tct gcg gtc tat tat tgt
gca aga cgg cgg tat agg tcc tcc tat gct atg gac tac tgg ggt caa
gga acc tca gtc acc gtc tcc tca

M   Q   L   S   S   L   T   S   D   D   S   A   V   Y   Y   C   A
R   R   R   Y   R   S   S   Y   A   M   D   Y   W   G   Q   G   T
S   V   T   V   S   S
```

VL-Version Accession number U23047.1 GI:736419

```
1 gaaacaactg tgacccagtc tccagcatcc ctgtccgtgg ctacaggaga aaaagt-
cact

61 atcagatgca taaccaacac tgatattgat gatgatatga actggtacca gcagaag-
cca

121 ggggaacctc ctaagctcct tatttcagaa ggcaatactc ttcgtcctgg
agtcccatcc

181 cgattctcca gcagtggcta tggcactgat tttgttttta caattgaaaa
cacgctctca

241 gaagatgttg cagattactg ctgtttgcaa agtgataaca tgcctctcac
gttcggtgct

301 gggaccaagc tggagctgaa a
```

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1/1                                                 31/11
61/21                                               91/31
```

```
gaa aca act gtg acc cag tct cca gca tcc ctg tcc gtg gct aca gga
gaa aaa gtc act atc aga tgc ata acc aac act gat att gat gat gat
atg aac tgg tac cag cag aag cca

E   T   T   V   T   Q   S   P   A   S   L   S   V   A   T   G   E
K   V   T   I   R   C   I   T   N   T   D   I   D   D   D   M   N
W   Y   Q   Q   K   P

121/41                                  151/51
181/61                                  211/71

ggg gaa cct cct aag ctc ctt att tca gaa ggc aat act ctt cgt cct
gga gtc cca tcc cga ttc tcc agc agt ggc tat ggc act gat ttt gtt
ttt aca att gaa aac acg ctc tca

G   E   P   P   K   L   L   I   S   E   G   N   T   L   R   P   G
V   P   S   R   F   S   S   S   G   Y   G   T   D   F   V   F   T
I   E   N   T   L   S

241/81                                  271/91
301/101

gaa gat gtt gca gat tac tgc tgt ttg caa agt gat aac atg cct ctc
acg ttc ggt gct ggg acc aag ctg gag ctg aaa

E   D   V   A   D   Y   C   C   L   Q   S   D   N   M   P   L   T
        F   G   A   G   T   K   L   E   L   K
```

1. anti-herpes glycoprotein B (ligands specific for herpes viral coat proteins) Ohlin,M. et al., Mol. Immunol. 33 (1), 47-56 (1996), sequence dadabase: National Center for Biological Resources, (NCBI, accessible through http://www.ncbi.nlm.nih.gov/)

VH-Version Accession number L37310.1 GI:845513

```
1 cagctgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cttga-
gactc

61 tcctgtgcag cctctgggtt cattttcagt gagtatgata tgcactgggt
ccgccaggct

121 ccaggcaagg ggctgcagtg ggtggcagtt atatcagttg atggaagtga taaa-
cactac

181 gcagactccg tgaagggccg attcaccatc tccagagaca attcccagaa
catgttgttt

241 ctacaaatgg acagcctgag aggtgacgac acggctgttt attattgtgc gaga-
gatgga

301 aaaagtttga atggttattc cggcttgatt gactactggg gccagggatc cttagt-
cacc

361 gtctcctca
```

```
1/1                                                 31/11
61/21                                               91/31

cag ctg cag ctg gtg gag tct ggg gga ggc gtg gtc cag cct ggg agg
tcc ttg aga ctc tcc tgt gca gcc tct ggg ttc att ttc agt gag tat
gat atg cac tgg gtc cgc cag gct

Q   L   Q   L   V   E   S   G   G   G   V   V   Q   P   G   R   S
L   R   L   S   C   A   A   S   G   F   I   F   S   E   Y   D   M
H   W   V   R   Q   A

121/41                                              151/51
181/61                                              211/71

cca ggc aag ggg ctg cag tgg gtg gca gtt ata tca gtt gat gga agt
gat aaa cac tac gca gac tcc gtg aag ggc cga ttc acc atc tcc aga
gac aat tcc cag aac atg ttg ttt

P   G   K   G   L   Q   W   V   A   V   I   S   V   D   G   S   D
K   H   Y   A   D   S   V   K   G   R   F   T   I   S   R   D   N
S   Q   N   M   L   F

241/81                                              271/91
301/101                                             331/111

cta caa atg gac agc ctg aga ggt gac gac acg gct gtt tat tat tgt
gcg aga gat gga aaa agt ttg aat ggt tat tcc ggc ttg att gac tac
tgg ggc cag gga tcc tta gtc acc

L   Q   M   D   S   L   R   G   D   D   T   A   V   Y   Y   C   A
R   D   G   K   S   L   N   G   Y   S   G   L   I   D   Y   W   G
Q   G   S   L   V   T

361/121

gtc tcc tca

V   S   S
```

VL-Version Accession number L37301.1 GI:845517

```
1 gaaattgtgt tgacgcagtc tccagccacc ctgtctttgt ctccagggga aa-
gagccacc

61 ctctcctgca gggccagtca gagtgttggc agctccttag cctggtacca aca-
gaaacct

121 ggccaggctc ccaggctcct cgtctatgat acatccaaca gggccactgg
catcccagcc

181 aggttcaatg gcagtgggtc tgggacagac ttcactctca ccatcagcag ccta-
gagcct

241 gaagattttg cagattatta ctgtcaacag cgaagcgagt ggcctctcac
tttcggcgga

301 gggaccaagg tggagatcaa a
```

```
1/1                                                 31/11
61/21                                               91/31

gaa att gtg ttg acg cag tct cca gcc acc ctg tct ttg tct cca ggg
gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt gtt ggc agc tcc
tta gcc tgg tac caa cag aaa cct

E   I   V   L   T   Q   S   P   A   T   L   S   L   S   P   G   E
R   A   T   L   S   C   R   A   S   Q   S   V   G   S   S   L   A
W   Y   Q   Q   K   P

121/41                                              151/51
181/61                                              211/71

ggc cag gct ccc agg ctc ctc gtc tat gat aca tcc aac agg gcc act
ggc atc cca gcc agg ttc aat ggc agt ggg tct ggg aca gac ttc act
ctc acc atc agc agc cta gag cct

G   Q   A   P   R   L   L   V   Y   D   T   S   N   R   A   T   G
I   P   A   R   F   N   G   S   G   S   G   T   D   F   T   L   T
I   S   S   L   E   P

241/81                                              271/91
301/101

gaa gat ttt gca gat tat tac tgt caa cag cga agc gag tgg cct ctc
act ttc ggc gga ggg acc aag gtg gag atc aaa

E   D   F   A   D   Y   Y   C   Q   Q   R   S   E   W   P   L   T
F   G   G   G   T   K   V   E   I   K
```

2. Anti-glycoprotein D (ligands specific for viral coat proteins of HSV-1) Schellekens,G.A., Submitted to the sequence dadabaseof the National Center for Biological Resources, (NCBI, accessible through http://www.ncbi.nlm.nih.gov/) at 01-NOV-1993)

VH-Version Accession number X75537.1 GI:414141

```
1 gagtcgggac ctggcctggt gaaaccttct caatctctgt ccctcacctg
cactgtctct

61 ggctcctcaa tcaccagtga ttatgcctgg acctggatct ggcagtttcc aggaaa-
caaa

121 ctggagtgga tgggctacat aagctacatt ggtgccacta gctacaaccc
ctctctccaa

181 agtcgaatct ctatcactcg agacacctcc aagaaccatt tcttcctaca gttga-
attct

241 gtgaccactg aggacacagc cacatattac tgtgcacgag aggggtcttg
gttcttcggt
```

```
301 gtctggggcg cagggaccac ggtcaccgtc tcctca


1/1                                         31/11
61/21                                       91/31

gag tcg gga cct ggc ctg gtg aaa cct tct caa tct ctg tcc ctc acc
tgc act gtc tct ggc tcc tca atc acc agt gat tat gcc tgg acc tgg
atc tgg cag ttt cca gga aac aaa

E   S   G   P   G   L   V   K   P   S   Q   S   L   S   L   T   C
T   V   S   G   S   S   I   T   S   D   Y   A   W   T   W   I   W
Q   F   P   G   N   K

121/41                                      151/51
181/61                                      211/71

ctg gag tgg atg ggc tac ata agc tac att ggt gcc act agc tac aac
ccc tct ctc caa agt cga atc tct atc act cga gac acc tcc aag aac
cat ttc ttc cta cag ttg aat tct

L   E   W   M   G   Y   I   S   Y   I   G   A   T   S   Y   N   P
S   L   Q   S   R   I   S   I   T   R   D   T   S   K   N   H   F
F   L   Q   L   N   S

241/81                                      271/91
301/101                                     331/111

gtg acc act gag gac aca gcc aca tat tac tgt gca cga gag ggg tct
tgg ttc ttc ggt gtc tgg ggc gca ggg acc acg gtc acc gtc tcc tca

V   T   T   E   D   T   A   T   Y   Y   C   A   R   E   G   S   W
F   F   G   V   W   G   A   G   T   T   V   T   V   S   S
```

VL-Version Accession number X75536.1 GI:414143

```
1 gtgatgaccc agtctccact ctccctgcct gtcagtcttg gagatcaagc
ctccatctct

61 tgcagatcta gtcagagcct tgtacacact aatggaaaca cctatttaca
ttggtacctg

121 cagaagccag gccagtctcc aaaggtcctg atctacaaag tttccacccg
attttctggg

181 gtcccagaca ggttcagtgg cagtggatca gggacagatt tcacattcaa gatcag-
caga

241 gtggaggctg aggatctggg agtttatttc tgctctcaaa gtacatatgt
tccattcacg

301 ttcggctcgg ggacaaagtt ggaaataaaa cgg
```

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1/1                                                 31/11
61/21                                               91/31

gtg atg acc cag tct cca ctc tcc ctg cct gtc agt ctt gga gat caa
gcc tcc atc tct tgc aga tct agt cag agc ctt gta cac act aat gga
aac acc tat tta cat tgg tac ctg

V   M   T   Q   S   P   L   S   L   P   V   S   L   G   D   Q   A
S   I   S   C   R   S   S   Q   S   L   V   H   T   N   G   N   T
Y   L   H   W   Y   L

121/41                                              151/51
181/61                                              211/71

cag aag cca ggc cag tct cca aag gtc ctg atc tac aaa gtt tcc acc
cga ttt tct ggg gtc cca gac agg ttc agt ggc agt gga tca ggg aca
gat ttc aca ttc aag atc agc aga

Q   K   P   G   Q   S   P   K   V   L   I   Y   K   V   S   T   R
F   S   G   V   P   D   R   F   S   G   S   G   S   G   T   D   F
T   F   K   I   S   R

241/81                                              271/91
301/101                                             331/111

gtg gag gct gag gat ctg gga gtt tat ttc tgc tct caa agt aca tat
gtt cca ttc acg ttc ggc tcg ggg aca aag ttg gaa ata aaa cgg

V   E   A   E   D   L   G   V   Y   F   C   S   Q   S   T   Y   V
P   F   T   F   G   S   G   T   K   L   E   I   K   R
```

3. <u>anti-hepatitis B virus S antigen (ligands specific for viral coat proteins of hepatitis B virus)</u> Ryu,C.J., et al. , Gene 144 (2), 313-314 (1994) Sequence dadabase: National Center for Biological Resources, (NCBI, accessible through http://www.ncbi.nlm.nih.gov/)

VH-Version Accession number L25332.1 GI:437012

```
1 gaggttcagc tgcaacaatc tggacctgag ctggtgaaac ctggggcctc agtgaa-
gata

61 tcctgcaagg cttctggata tacattcact gactacaaca ttcagtgggt gaagca-
gagc

121 catggaaaga gccttgagtg gattggatat atttatcctt acactggtgg
tactggctac

181 agccagaagt tcaagagcaa ggccacattg actgtagaca atttctccag ca-
cagcctat

241 atggaactcc gcagcctgac atctgaggac tctgcagtct attactgtgc aa-
gaaactat

301 ggttacgacg agtctgctta ctggggccaa gggactctgg tcactgtctc tgca
```

```
1/1                                                 31/11
61/21                                               91/31

gag gtt cag ctg caa caa tct gga cct gag ctg gtg aaa cct ggg gcc
tca gtg aag ata tcc tgc aag gct tct gga tat aca ttc act gac tac
aac att cag tgg gtg aag cag agc

E   V   Q   L   Q   Q   S   G   P   E   L   V   K   P   G   A   S
V   K   I   S   C   K   A   S   G   Y   T   F   T   D   Y   N   I
Q   W   V   K   Q   S

121/41                                              151/51
181/61                                              211/71

cat gga aag agc ctt gag tgg att gga tat att tat cct tac act ggt
ggt act ggc tac agc cag aag ttc aag agc aag gcc aca ttg act gta
gac aat ttc tcc agc aca gcc tat

H   G   K   S   L   E   W   I   G   Y   I   Y   P   Y   T   G   G
T   G   Y   S   Q   K   F   K   S   K   A   T   L   T   V   D   N
F   S   S   T   A   Y

241/81                                              271/91
301/101                                             331/111

atg gaa ctc cgc agc ctg aca tct gag gac tct gca gtc tat tac tgt
gca aga aac tat ggt tac gac gag tct gct tac tgg ggc caa ggg act
ctg gtc act gtc tct gca

M   E   L   R   S   L   T   S   E   D   S   A   V   Y   Y   C   A
R   N   Y   G   Y   D   E   S   A   Y   W   G   Q   G   T   L   V
T   V   S   A
```

VL-Version Accession number L25333.1 GI:437013

```
1 gacattgtgc tgacccaatc tccagcttct ttggctgtgt ctctagggca
gagggccacc

61 atctcctgca gagccagcga aagtgttgat aattatggca ttagttttat
gaactggttc

121 caacagaaac caggacagcc acccaaactc ctcatctata ctgcatccaa ccaag-
gatcc

181 ggggtccctg ccaggtttag tggcagtggg tctgggacag acttcagcct caa-
catccat

241 cctatggagg tggatgatac tgcaatgtat ttctgtcagc aaactaagga
ggttccgtac

301 acgttcggag gggggaccaa gctggaaata aaacgg
```

```
1/1                                                 31/11
61/21                                               91/31

gac att gtg ctg acc caa tct cca gct tct ttg gct gtg tct cta ggg
cag agg gcc acc atc tcc tgc aga gcc agc gaa agt gtt gat aat tat
ggc att agt ttt atg aac tgg ttc

D   I   V   L   T   Q   S   P   A   S   L   A   V   S   L   G   Q
R   A   T   I   S   C   R   A   S   E   S   V   D   N   Y   G   I
S   F   M   N   W   F

121/41                                              151/51
181/61                                              211/71

caa cag aaa cca gga cag cca ccc aaa ctc ctc atc tat act gca tcc
aac caa gga tcc ggg gtc cct gcc agg ttt agt ggc agt ggg tct ggg
aca gac ttc agc ctc aac atc cat

Q   Q   K   P   G   Q   P   P   K   L   L   I   Y   T   A   S   N
Q   G   S   G   V   P   A   R   F   S   G   S   G   S   G   T   D
F   S   L   N   I   H

241/81                                              271/91
301/101                                             331/111

cct atg gag gtg gat gat act gca atg tat ttc tgt cag caa act aag
gag gtt ccg tac acg ttc gga ggg ggg acc aag ctg gaa ata aaa cgg

P   M   E   V   D   D   T   A   M   Y   F   C   Q   Q   T   K   E

V   P   Y   T   F   G   G   G   T   K   L   E   I   K   R
```

4. anti- anti-hepatitis C virus envelope protein (ligands specific for viral coat proteins of hepatitis C virus) Chan,S.W., J. Gen. Virol. 77 (Pt 10), 2531-2539 (1996), Sequence dadabase: National Center for Biological Resources, (NCBI, accessible through http://www.ncbi.nlm.nih.gov/) Medline Accession numberr 97042287

VH-Version Accession number X97554.1 GI:1657322

```
2 atggcccag gtacagctgc agcagtcagg gggaggcctg gtcaagcctg ggggatccct

61 gagactctcc tgtgcaggct ctggattcag catcggagac tatagcatga
actgggtccg

121 ccaggctcca gggaaggggc tggagtgggt cgcgtccatc agtcctgata
gtgtttatag

181 acactatgca gactcactga ggggccgatt caccatttcc agagacaacg ccag-
gaactc

241 actgtttctg caattgacca ggctgacagc cgacgacacg gctgtgtatt
ggtgtgcgag

301 acaccgacct acatatggtg tctactatta tggtatggac gtctggggcc
acgggaccac
```

```
361 ggtcaccgtg tcga


1/1                                             31/11
61/21                                           91/31

atg gcc cag gta cag ctg cag cag tca ggg gga ggc ctg gtc aag cct
ggg gga tcc ctg aga ctc tcc tgt gca ggc tct gga ttc agc atc gga
gac tat agc atg aac tgg gtc cgc

M   A   Q   V   Q   L   Q   Q   S   G   G   G   L   V   K   P   G
G   S   L   R   L   S   C   A   G   S   G   F   S   I   G   D   Y
S   M   N   W   V   R

121/41                                          151/51
181/61                                          211/71

cag gct cca ggg aag ggg ctg gag tgg gtc gcg tcc atc agt cct gat
agt gtt tat aga cac tat gca gac tca ctg agg ggc cga ttc acc att
tcc aga gac aac gcc agg aac tca

Q   A   P   G   K   G   L   E   W   V   A   S   I   S   P   D   S
V   Y   R   H   Y   A   D   S   L   R   G   R   F   T   I   S   R
D   N   A   R   N   S

241/81                                          271/91
301/101                                         331/111

ctg ttt ctg caa ttg acc agg ctg aca gcc gac gac acg gct gtg tat
tgg tgt gcg aga cac cga cct aca tat ggt gtc tac tat tat ggt atg
gac gtc tgg ggc cac ggg acc acg

L   F   L   Q   L   T   R   L   T   A   D   D   T   A   V   Y   W
C   A   R   H   R   P   T   Y   G   V   Y   Y   Y   G   M   D   V
W   G   H   G   T   T

361/121

gtc acc gtg tcg a

V   T   V   S
```

VL-Version Accession number X97555.1 GI:1657328

```
1 gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtagggga cagagt-
cacc

61 atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaag-
cca

121 gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg
ggtcccatca

181 aggttcagcg gcagtggatc tgggacacat ttcactctca ctatcagcag
cctgcagcct
```

```
241 gaagactttg caacttacta ttgtcaacag gctaacagtt tccccctcac
tttcggcgga

301 gggaccaagg tggaaatcaa acgtgcggcc


1/1                                             31/11
61/21                                           91/31

gac atc cag atg acc cag tct cca tcc tcc ctg tct gca tct gta ggg
gac aga gtc acc atc act tgt cgg gcg agt cag ggt att agc agc tgg
tta gcc tgg tat cag cag aag cca

D   I   Q   M   T   Q   S   P   S   S   L   S   A   S   V   G   D
R   V   T   I   T   C   R   A   S   Q   G   I   S   S   W   L   A
W   Y   Q   Q   K   P

121/41                                          151/51
181/61                                          211/71

ggg aaa gcc cct aag ctc ctg atc tat gct gca tcc agt ttg caa agt
ggg gtc cca tca agg ttc agc ggc agt gga tct ggg aca cat ttc act
ctc act atc agc agc ctg cag cct

G   K   A   P   K   L   L   I   Y   A   A   S   S   L   Q   S   G
V   P   S   R   F   S   G   S   G   S   G   T   H   F   T   L   T
I   S   S   L   Q   P

241/81                                          271/91
301/101

gaa gac ttt gca act tac tat tgt caa cag gct aac agt ttc ccc ctc
act ttc ggc gga ggg acc aag gtg gaa atc aaa cgt gcg gcc

E   D   F   A   T   Y   Y   C   Q   Q   A   N   S   F   P   L   T
F   G   G   G   T   K   V   E   I   K   R   A   A
```

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 38005-0121

In re patent application of

Robert KONTERMANN et al.

Serial No. US 09/288,719 Group Art Unit: 1632

Filed: April 09, 1999 Examiner: A. Beckerleg

For: SINGLE-CHAIN MULTIPLE ANTIGEN-BINDING MOLECULE, ITS PREPARATION AND USE

EXHIBIT H

Sequences of single chain multiple antigen binding molecules

Examples of single chain multiple antigen binding molecules (ScMAB) comprise inter alia:

1. ScMAB anti-Tumor x anti CD3 (based on sequences with the accession number S77598.1 / S77599.1 and AF000359.1 / AF000358.1) for the retargeting of cytotoxic T lymphocytes to tumor cells (anti-CD3 antibody specific for cytotoxic T lymphocytes, Gilliland,L.K., et al. Tissue Antigens 47 (1), 1-20 (1996) Sequence dadabase: National Center for Biological Resources; anti-tumor antibody (against ovarina, cerix, breast and colon carcinoma, i.e. specific for membrane structures of tumor cells, Chen,P.F., et al., Hum. Antibodies Hybridomas 5 (3-4), 131-142 (1994), sequence dadabase: National Center for Biological Resources, (NCBI, accessible through http://www.ncbi.nlm.nih.gov/)).

Structure of the ScMAB:

# Nucleic Acid	Function
1-66	pelB signal sequence
67-468	VH anti-Tumor
469-483	Linker L1

484-804	VL anti-CD3
805-849	Peptide Linker P
850-1209	VH anti-CD3
1210-1224	Linker L2
1225-1545	VL anti-Tumor
1546-1548	Stop codon

ATGAAATACCTATTGCCTACGGCAGCCGCTGGATTGTTATTACTCGCGGC
CCAGCCGGCCATGGCCcaggtgcagctggtgcagtctggggctgaggtga
agaagcctggggcctcagtgaaggtttcctgcaaggcatctggatacacc
ttcaccagctactatatgcactgggtcgaacaggcccctggacaagggct
tgagtggatgggaataatcaaccctagtggtggtagcacaagctacgcac
agaagttccagggcagagtcaccatgaccagggacacgtccacgagcaca
gtctacatggagctgagcagcctgagatctgaggacacggccgtgtatta
ctgtgctagagaggatgggcctacagctatggccacaagggccgacctaa
cgacaacatactactactactacggtatggacgtctggggccaagggacc
acggtcaccgtctcctcaGGCGGTGGCGGATCGgacatagtgctgactca
gactccagccactctgtctctaattcctggagaaagagtcacaatgacct
gtaagaccagtcagaatattggcacaatcttacactggtatcaccaaaaa
ccaaaggaggctccaagggctctcatcaagtatgcttcgcagtccattcc
tgggatcccctccagattcagtggcagtggttcggaaacagatttcactc
tcagcatcaataacctggagcctgatgatatcggaatttattactgtcaa
caaagtagaagctggcctgtcacgttcggtcctggcaccaagctggagat
aaaaGGAGGCGGTGGCAGCGGTGGGCGCGCCTCGGGCGGAGGTGGCTCAc
aggtcaagctgcagcagtccggttctgaactagggaaacctggggcctca
gtgaaactgtcctgcaagacttcaggctacatattcacagatcactatat
ttcttgggtgaaacagaagcctggagaaagcctgcagtggataggaaatg
tttatggtggaaatggtggtacaagctacaatcaaaaattccagggcaag
gccacactgactgtagataaaatctctagcacagcctacatggaactcag
cagcctgacatctgaggattctgccatctattactgtgcaagaaggccgg
tagcgacgggccatgctatggactactggggtcaggggatccaagttacc
gtctcctcaGGAGGCGGGGGTTCGgatatcgagctcccaccctcggtgtc
agtgtccctaggacagatggccaggatcacctgctctggagaagcattgc
caaaaaaatatgcttattggtaccagcagaagccaggccagttccctgtg

ctggtgatatataaagacagcgagagggcctcagggatccctgagcgatt

ctctggctccagctcagggacaatagtcacattgaccatcagtggagtcc

aggcagaagacgaggctgactattactgtctatcagcagacagcagtggt

acttatggcgggtggttcggcggagggaccaagctgaccgtcctaTAA

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1/1                                                 31/11
61/21                                               91/31

ATG AAA TAC CTA TTG CCT ACG GCA GCC GCT GGA TTG TTA TTA CTC GCG
GCC CAG CCG GCC ATG GCC cag gtg cag ctg gtg cag tct ggg gct gag
gtg aag aag cct ggg gcc tca gtg

M   K   Y   L   L   P   T   A   A   A   G   L   L   L   L   A   A
Q   P   A   M   A   Q   V   Q   L   V   Q   S   G   A   E   V   K
K   P   G   A   S   V

121/41                                              151/51
181/61                                              211/71

aag gtt tcc tgc aag gca tct gga tac acc ttc acc agc tac tat atg
cac tgg gtc gaa cag gcc cct gga caa ggg ctt gag tgg atg gga ata
atc aac cct agt ggt ggt agc aca

K   V   S   C   K   A   S   G   Y   T   F   T   S   Y   Y   M   H
W   V   E   Q   A   P   G   Q   G   L   E   W   M   G   I   I   N
P   S   G   G   S   T

241/81                                              271/91
301/101                                             331/111

agc tac gca cag aag ttc cag ggc aga gtc acc atg acc agg gac acg
tcc acg agc aca gtc tac atg gag ctg agc agc ctg aga tct gag gac
acg gcc gtg tat tac tgt gct aga

S   Y   A   Q   K   F   Q   G   R   V   T   M   T   R   D   T   S
T   S   T   V   Y   M   E   L   S   S   L   R   S   E   D   T   A
V   Y   Y   C   A   R

361/121                                             391/131
421/141                                             451/151

gag gat ggg cct aca gct atg gcc aca agg gcc gac cta acg aca aca
tac tac tac tac tac ggt atg gac gtc tgg ggc caa ggg acc acg gtc
acc gtc tcc tca GGC GGT GGC GGA

E   D   G   P   T   A   M   A   T   R   A   D   L   T   T   T   Y
Y   Y   Y   Y   G   M   D   V   W   G   Q   G   T   T   V   T   V
S   S   G   G   G   G

481/161                                             511/171
541/181                                             571/191
```

```
TCG gac ata gtg ctg act cag act cca gcc act ctg tct cta att cct
gga gaa aga gtc aca atg acc tgt aag acc agt cag aat att ggc aca
atc tta cac tgg tat cac caa aaa

S   D   I   V   L   T   Q   T   P   A   T   L   S   L   I   P   G
E   R   V   T   M   T   C   K   T   S   Q   N   I   G   T   I   L
H   W   Y   H   Q   K

601/201                                     631/211
661/221                                     691/231

cca aag gag gct cca agg gct ctc atc aag tat gct tcg cag tcc att
cct ggg atc ccc tcc aga ttc agt ggc agt ggt tcg gaa aca gat ttc
act ctc agc atc aat aac ctg gag

P   K   E   A   P   R   A   L   I   K   Y   A   S   Q   S   I   P
G   I   P   S   R   F   S   G   S   G   S   E   T   D   F   T   L
S   I   N   N   L   E

721/241                                     751/251
781/261                                     811/271

cct gat gat atc gga att tat tac tgt caa caa agt aga agc tgg cct
gtc acg ttc ggt cct ggc acc aag ctg gag ata aaa GGA GGC GGT GGC
AGC GGT GGG CGC GCC TCG GGC GGA

P   D   D   I   G   I   Y   Y   C   Q   Q   S   R   S   W   P   V
T   F   G   P   G   T   K   L   E   I   K   G   G   G   G   S   G
G   R   A   S   G   G

841/281                                     871/291
901/301                                     931/311

GGT GGC TCA cag gtc aag ctg cag cag tcc ggt tct gaa cta ggg aaa
cct ggg gcc tca gtg aaa ctg tcc tgc aag act tca ggc tac ata ttc
aca gat cac tat att tct tgg gtg

G   G   S   Q   V   K   L   Q   Q   S   G   S   E   L   G   K   P
G   A   S   V   K   L   S   C   K   T   S   G   Y   I   F   T   D
H   Y   I   S   W   V

961/321                                     991/331
1021/341                                    1051/351

aaa cag aag cct gga gaa agc ctg cag tgg ata gga aat gtt tat ggt
gga aat ggt ggt aca agc tac aat caa aaa ttc cag ggc aag gcc aca
ctg act gta gat aaa atc tct agc

K   Q   K   P   G   E   S   L   Q   W   I   G   N   V   Y   G   G
N   G   G   T   S   Y   N   Q   K   F   Q   G   K   A   T   L   T
V   D   K   I   S   S

1081/361                                    1111/371
1141/381                                    1171/391

aca gcc tac atg gaa ctc agc agc ctg aca tct gag gat tct gcc atc
tat tac tgt gca aga agg ccg gta gcg acg ggc cat gct atg gac tac
tgg ggt cag ggg atc caa gtt acc
```

```
T   A   Y   M   E   L   S   S   L   T   S   E   D   S   A   I   Y
Y   C   A   R   R   P   V   A   T   G   H   A   M   D   Y   W   G
Q   G   I   Q   V   T

1201/401                                        1231/411
1261/421                                        1291/431

gtc tcc tca GGA GGC GGG GGT TCG gat atc gag ctc cca ccc tcg gtg
tca gtg tcc cta gga cag atg gcc agg atc acc tgc tct gga gaa gca
ttg cca aaa aaa tat gct tat tgg

V   S   S   G   G   G   G   S   D   I   E   L   P   P   S   V   S
V   S   L   G   Q   M   A   R   I   T   C   S   G   E   A   L   P
K   K   Y   A   Y   W

1321/441                                        1351/451
1381/461                                        1411/471

tac cag cag aag cca ggc cag ttc cct gtg ctg gtg ata tat aaa gac
agc gag agg gcc tca ggg atc cct gag cga ttc tct ggc tcc agc tca
ggg aca ata gtc aca ttg acc atc

Y   Q   Q   K   P   G   Q   F   P   V   L   V   I   Y   K   D   S
E   R   A   S   G   I   P   E   R   F   S   G   S   S   S   G   T
I   V   T   L   T   I

1441/481                                        1471/491
1501/501                                        1531/511

agt gga gtc cag gca gaa gac gag gct gac tat tac tgt cta tca gca
gac agc agt ggt act tat ggc ggg tgg ttc ggc gga ggg acc aag ctg
acc gtc cta TAA

S   G   V   Q   A   E   D   E   A   D   Y   Y   C   L   S   A   D
S   S   G   T   Y   G   G   W   F   G   G   G   T   K   L   T   V
L   *
```

2. ScMAB anti-Tumor x anti Anti-FC-γ receptor I (based on sequences with the accession number Seq. S77598.1 / S77599.1 and Z50001.1 / Z50002.1) for the retargeting of NK cells and macrophages to tumor cells (Anti-FC-γ receptor I-antibody specific for NK cells, macrophages, Tempest, P.R., submitted to the National Center for Biological Resources 30-JUN-1995; and anti-tumor antibody specific for ovarina, cerix, breast and colon carcinoma, i.e. specific for membrane structures of tumor cells, Chen,P.F., et al., Hum. Antibodies Hybridomas 5 (3-4), 131-142 (1994), Sequence dadabase: National Center for Biological Resources, (NCBI, accessible through http://www.ncbi.nlm.nih.gov/).

Structure of the ScMAB:

# Nucleic Acid	Function
1-66	pelB signal sequence
67-468	VH anti-Tumor
469-483	Linker L1
484-819	VL anti-FcgRI
820-864	Peptide Linker P
865-1224	VH anti-FcgRI
1225-1239	Linker L2
1240-1561	VL anti-Tumor
1562-1564	Stop codon

ATGAAATACCTATTGCCTACGGCAGCCGCTGGATTGTTATTACTCGCGGC
CCAGCCGGCCATGGCCcaggtgcagctggtgcagtctggggctgaggtga
agaagcctggggcctcagtgaaggtttcctgcaaggcatctggatacacc
ttcaccagctactatatgcactgggtcgaacaggcccctggacaagggct
tgagtggatgggaataatcaaccctagtggtggtagcacaagctacgcac
agaagttccagggcagagtcaccatgaccagggacacgtccacgagcaca
gtctacatggagctgagcagcctgagatctgaggacacggccgtgtatta
ctgtgctagagaggatgggcctacagctatggccacaagggccgacctaa
cgacaacatactactactactacggtatggacgtctggggccaagggacc
acggtcaccgtctcctcaGGCGGTGGCGGATCGgacatccagctgaccca
gagcccaagcagcctgagcgccagcgtgggtgacagagtgaccatcacct
gtaagtccagtcaaagtgttttatacagttcaaatcagaagaactacttg
gcctggtaccagcagaagccaggtaaggctccaaagctgctgatctactg
ggcatccactagggaatctggtgtgccaagcagattcagcggtagcggta
gcggtaccgacttcaccttcaccatcagcagcctccagccagaggacatc
gccacctactactgccatcaatacctctcctcgtggacgttcggccaagg
gaccaaggtggaaatcaaaGGAGGCGGTGGCAGCGGTGGGCGCGCCTCGG
GCGGAGGTGGCTCAcaggtccaactgcaggagagcggtccaggtcttgtg
agacctagccagaccctgagcctgacctgcaccgtgtctggcttcatttt
cagcgacaattacatgtattgggtgagacagccacctggacgaggtcttg
agtggattggaaccattagtgatggtggtagttacacctactatcctgac

agtgtgaaggggagagtgacaatgctgagagacaccagcaagaaccagtt

cagcctgagactcagcagcgtgacagccgccgacaccgcggtctattatt

gtgcaagaggctactataggtacgaggggctatggactactggggccaa

gggtccttggtcaccgtctcctcaGGAGGCGGGGGTTCGgatatcgagct

cccaccctcggtgtcagtgtccctaggacagatggccaggatcacctgct

ctggagaagcattgccaaaaaaatatgcttattggtaccagcagaagcca

ggccagttccctgtgctggtgatatataaagacagcgagagggcctcagg

gatccctgagcgattctctggctccagctcagggacaatagtcacattga

ccatcagtggagtccaggcagaagacgaggctgactattactgtctatca

gcagacagcagtggtacttatggcgggtggttcggcggagggaccaagct

gaccgtcctaTAA

1/1 31/11
61/21 91/31

ATG AAA TAC CTA TTG CCT ACG GCA GCC GCT GGA TTG TTA TTA CTC GCG
GCC CAG CCG GCC ATG GCC cag gtg cag ctg gtg cag tct ggg gct gag
gtg aag aag cct ggg gcc tca gtg

M K Y L L P T A A A G L L L L A A
Q P A M A Q V Q L V Q S G A E V K
K P G A S V

121/41 151/51
181/61 211/71

aag gtt tcc tgc aag gca tct gga tac acc ttc acc agc tac tat atg
cac tgg gtc gaa cag gcc cct gga caa ggg ctt gag tgg atg gga ata
atc aac cct agt ggt ggt agc aca

K V S C K A S G Y T F T S Y Y M H
W V E Q A P G Q G L E W M G I I N
P S G G S T

241/81 271/91
301/101 331/111

agc tac gca cag aag ttc cag ggc aga gtc acc atg acc agg gac acg
tcc acg agc aca gtc tac atg gag ctg agc agc ctg aga tct gag gac
acg gcc gtg tat tac tgt gct aga

S Y A Q K F Q G R V T M T R D T S
T S T V Y M E L S S L R S E D T A
V Y Y C A R

361/121 391/131
421/141 451/151

```
gag gat ggg cct aca gct atg gcc aca agg gcc gac cta acg aca aca
tac tac tac tac tac ggt atg gac gtc tgg ggc caa ggg acc acg gtc
acc gtc tcc tca GGC GGT GGC GGA

E   D   G   P   T   A   M   A   T   R   A   D   L   T   T   T   Y
Y   Y   Y   Y   G   M   D   V   W   G   Q   G   T   T   V   T   V
S   S   G   G   G   G

481/161                                     511/171
541/181                                     571/191

TCG gac atc cag ctg acc cag agc cca agc agc ctg agc gcc agc gtg
ggt gac aga gtg acc atc acc tgt aag tcc agt caa agt gtt tta tac
agt tca aat cag aag aac tac ttg

S   D   I   Q   L   T   Q   S   P   S   S   L   S   A   S   V   G
D   R   V   T   I   T   C   K   S   S   Q   S   V   L   Y   S   S
N   Q   K   N   Y   L

601/201                                     631/211
661/221                                     691/231

gcc tgg tac cag cag aag cca ggt aag gct cca aag ctg ctg atc tac
tgg gca tcc act agg gaa tct ggt gtg cca agc aga ttc agc ggt agc
ggt agc ggt acc gac ttc acc ttc

A   W   Y   Q   Q   K   P   G   K   A   P   K   L   L   I   Y   W
A   S   T   R   E   S   G   V   P   S   R   F   S   G   S   G   S
G   T   D   F   T   F

721/241                                     751/251
781/261                                     811/271

acc atc agc agc ctc cag cca gag gac atc gcc acc tac tac tgc cat
caa tac ctc tcc tcg tgg acg ttc ggc caa ggg acc aag gtg gaa atc
aaa GGA GGC GGT GGC AGC GGT GGG

T   I   S   S   L   Q   P   E   D   I   A   T   Y   Y   C   H   Q
Y   L   S   S   W   T   F   G   Q   G   T   K   V   E   I   K   G
G   G   G   S   G   G

841/281                                     871/291
901/301                                     931/311

CGC GCC TCG GGC GGA GGT GGC TCA cag gtc caa ctg cag gag agc ggt
cca ggt ctt gtg aga cct agc cag acc ctg agc ctg acc tgc acc gtg
tct ggc ttc att ttc agc gac aat

R   A   S   G   G   G   G   S   Q   V   Q   L   Q   E   S   G   P
G   L   V   R   P   S   Q   T   L   S   L   T   C   T   V   S   G
F   I   F   S   D   N

961/321                                     991/331
1021/341                                    1051/351

tac atg tat tgg gtg aga cag cca cct gga cga ggt ctt gag tgg att
gga acc att agt gat ggt ggt agt tac acc tac tat cct gac agt gtg
aag ggg aga gtg aca atg ctg aga
```

```
Y   M   Y   W   V   R   Q   P   P   G   R   G   L   E   W   I   G
T   I   S   D   G   G   S   Y   T   Y   Y   P   D   S   V   K   G
R   V   T   M   L   R

1081/361                                        1111/371
1141/381                                        1171/391

gac acc agc aag aac cag ttc agc ctg aga ctc agc agc gtg aca gcc
gcc gac acc gcg gtc tat tat tgt gca aga ggc tac tat agg tac gag
ggg gct atg gac tac tgg ggc caa

D   T   S   K   N   Q   F   S   L   R   L   S   S   V   T   A   A
D   T   A   V   Y   Y   C   A   R   G   Y   Y   R   Y   E   G   A
M   D   Y   W   G   Q

1201/401                                        1231/411
1261/421                                        1291/431

ggg tcc ttg gtc acc gtc tcc tca GGA GGC GGG GGT TCG gat atc gag
ctc cca ccc tcg gtg tca gtg tcc cta gga cag atg gcc agg atc acc
tgc tct gga gaa gca ttg cca aaa

G   S   L   V   T   V   S   S   G   G   G   G   S   D   I   E   L
P   P   S   V   S   V   S   L   G   Q   M   A   R   I   T   C   S
G   E   A   L   P   K

1321/441                                        1351/451
1381/461                                        1411/471

aaa tat gct tat tgg tac cag cag aag cca ggc cag ttc cct gtg ctg
gtg ata tat aaa gac agc gag agg gcc tca ggg atc cct gag cga ttc
tct ggc tcc agc tca ggg aca ata

K   Y   A   Y   W   Y   Q   Q   K   P   G   Q   F   P   V   L   V
I   Y   K   D   S   E   R   A   S   G   I   P   E   R   F   S   G
S   S   S   G   T   I

1441/481                                        1471/491
1501/501                                        1531/511

gtc aca ttg acc atc agt gga gtc cag gca gaa gac gag gct gac tat
tac tgt cta tca gca gac agc agt ggt act tat ggc ggg tgg ttc ggc
gga ggg acc aag ctg acc gtc cta

V   T   L   T   I   S   G   V   Q   A   E   D   E   A   D   Y   Y
C   L   S   A   D   S   S   G   T   Y   G   G   W   F   G   G   G
T   K   L   T   V   L

1561/521

TAA

*
```

3. ScMAB anti-Tumor x anti-herpes virus glycoprotein B (based on sequences with the accession number Seq. S77598.1 / S77599.1 and L37310.1 / L37301.1) for the retargeting of herpes virus to tumor cells (anti-herpes glycoprotein B antibody specific for herpes viral coat proteins, Ohlin,M. et al., Mol. Immunol. 33 (1), 47-56 (1996), sequence dadabase: National Center for Biological Resources; and anti-tumor Antibody specific for ovarina, cerix, breast and colon carcinoma, i.e. specific for membrane structures of tumor cells, Chen,P.F., et al., Hum. Antibodies Hybridomas 5 (3-4), 131-142 (1994), Sequence dadabase: National Center for Biological Resources, (NCBI, accessible through http://www.ncbi.nlm.nih.gov/).

Structure of the ScMAB:

# Nucleic Acid	Function
1-66	pelB signal sequence
67-468	VH anti-Tumor
469-483	Linker L1
484-804	VL anti-herpes virus glycoprotein B
805-849	Peptide Linker P
850-1218	VH anti- herpes virus glycoprotein B
1219-1233	Linker L2
1234-1554	VL anti-Tumor
1555-1557	Stop codon

ATGAAATACCTATTGCCTACGGCAGCCGCTGGATTGTTATTACTCGCGGC
CCAGCCGGCCATGGCCcaggtgcagctggtgcagtctggggctgaggtga
agaagcctggggcctcagtgaaggtttcctgcaaggcatctggatacacc
ttcaccagctactatatgcactgggtcgaacaggcccctggacaagggct
tgagtggatgggaataatcaaccctagtggtggtagcacaagctacgcac
agaagttccagggcagagtcaccatgaccagggacacgtccacgagcaca
gtctacatggagctgagcagcctgagatctgaggacacggccgtgtatta
ctgtgctagagaggatgggcctacagctatggccacaagggccgacctaa
cgacaacatactactactactacggtatggacgtctggggccaagggacc
acggtcaccgtctcctcaGGCGGTGGCGGATCGgaaattgtgttgacgca
gtctccagccaccctgtctttgtctccaggggaaagagccaccctctcct

gcagggccagtcagagtgttggcagctccttagcctggtaccaacagaaa

cctggccaggctcccaggctcctcgtctatgatacatccaacagggccac

tggcatcccagccaggttcaatggcagtgggtctgggacagacttcactc

tcaccatcagcagcctagagcctgaagattttgcagattattactgtcaa

cagcgaagcgagtggcctctcactttcggcggagggaccaaggtggagat

caaaGGAGGCGGTGGCAGCGGTGGGCGCGCCTCGGGCGGAGGTGGCTCAc

agctgcagctggtggagtctgggggaggcgtggtccagcctgggaggtcc

ttgagactctcctgtgcagcctctgggttcattttcagtgagtatgatat

gcactgggtccgccaggctccaggcaaggggctgcagtgggtggcagtta

tatcagttgatggaagtgataaacactacgcagactccgtgaagggccga

ttcaccatctccagagacaattcccagaacatgttgtttctacaaatgga

cagcctgagaggtgacgacacggctgtttattattgtgcgagagatggaa

aaagtttgaatggttattccggcttgattgactactggggccagggatcc

ttagtcaccgtctcctcaGGAGGCGGGGGTTCGgatatcgagctcccacc

ctcggtgtcagtgtccctaggacagatggccaggatcacctgctctggag

aagcattgccaaaaaaatatgcttattggtaccagcagaagccaggccag

ttccctgtgctggtgatatataaagacagcgagagggcctcagggatccc

tgagcgattctctggctccagctcagggacaatagtcacattgaccatca

gtggagtccaggcagaagacgaggctgactattactgtctatcagcagac

agcagtggtacttatggcgggtggttcggcggagggaccaagctgaccgt

cctaTAA

1/1 31/11
61/21 91/31

ATG AAA TAC CTA TTG CCT ACG GCA GCC GCT GGA TTG TTA TTA CTC GCG
GCC CAG CCG GCC ATG GCC cag gtg cag ctg gtg cag tct ggg gct gag
gtg aag aag cct ggg gcc tca gtg

M K Y L L P T A A A G L L L L A A
Q P A M A Q V Q L V Q S G A E V K
K P G A S V

121/41 151/51
181/61 211/71

```
aag gtt tcc tgc aag gca tct gga tac acc ttc acc agc tac tat atg
cac tgg gtc gaa cag gcc cct gga caa ggg ctt gag tgg atg gga ata
atc aac cct agt ggt ggt agc aca

K   V   S   C   K   A   S   G   Y   T   F   T   S   Y   Y   M   H
W   V   E   Q   A   P   G   Q   G   L   E   W   M   G   I   I   N
P   S   G   G   S   T

241/81                                      271/91
301/101                                     331/111

agc tac gca cag aag ttc cag ggc aga gtc acc atg acc agg gac acg
tcc acg agc aca gtc tac atg gag ctg agc agc ctg aga tct gag gac
acg gcc gtg tat tac tgt gct aga

S   Y   A   Q   K   F   Q   G   R   V   T   M   T   R   D   T   S
T   S   T   V   Y   M   E   L   S   S   L   R   S   E   D   T   A
V   Y   Y   C   A   R

361/121                                     391/131
421/141                                     451/151

gag gat ggg cct aca gct atg gcc aca agg gcc gac cta acg aca aca
tac tac tac tac tac ggt atg gac gtc tgg ggc caa ggg acc acg gtc
acc gtc tcc tca GGC GGT GGC GGA

E   D   G   P   T   A   M   A   T   R   A   D   L   T   T   T   Y
Y   Y   Y   Y   G   M   D   V   W   G   Q   G   T   T   V   T   V
S   S   G   G   G   G

481/161                                     511/171
541/181                                     571/191

TCG gaa att gtg ttg acg cag tct cca gcc acc ctg tct ttg tct cca
ggg gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt gtt ggc agc
tcc tta gcc tgg tac caa cag aaa

S   E   I   V   L   T   Q   S   P   A   T   L   S   L   S   P   G
E   R   A   T   L   S   C   R   A   S   Q   S   V   G   S   S   L
A   W   Y   Q   Q   K

601/201                                     631/211
661/221                                     691/231

cct ggc cag gct ccc agg ctc ctc gtc tat gat aca tcc aac agg gcc
act ggc atc cca gcc agg ttc aat ggc agt ggg tct ggg aca gac ttc
act ctc acc atc agc agc cta gag

P   G   Q   A   P   R   L   L   V   Y   D   T   S   N   R   A   T
G   I   P   A   R   F   N   G   S   G   S   G   T   D   F   T   L
T   I   S   S   L   E

721/241                                     751/251
781/261                                     811/271

cct gaa gat ttt gca gat tat tac tgt caa cag cga agc gag tgg cct
ctc act ttc ggc gga ggg acc aag gtg gag atc aaa GGA GGC GGT GGC
AGC GGT GGG CGC GCC TCG GGC GGA
```

```
P   E   D   F   A   D   Y   Y   C   Q   Q   R   S   E   W   P   L
T   F   G   G   G   T   K   V   E   I   K   G   G   G   G   S   G
G   R   A   S   G   G
```

841/281 871/291
901/301 931/311

```
GGT GGC TCA cag ctg cag ctg gtg gag tct ggg gga ggc gtg gtc cag
cct ggg agg tcc ttg aga ctc tcc tgt gca gcc tct ggg ttc att ttc
agt gag tat gat atg cac tgg gtc
```

```
G   G   S   Q   L   Q   L   V   E   S   G   G   G   V   V   Q   P
G   R   S   L   R   L   S   C   A   A   S   G   F   I   F   S   E
Y   D   M   H   W   V
```

961/321 991/331
1021/341 1051/351

```
cgc cag gct cca ggc aag ggg ctg cag tgg gtg gca gtt ata tca gtt
gat gga agt gat aaa cac tac gca gac tcc gtg aag ggc cga ttc acc
atc tcc aga gac aat tcc cag aac
```

```
R   Q   A   P   G   K   G   L   Q   W   V   A   V   I   S   V   D
G   S   D   K   H   Y   A   D   S   V   K   G   R   F   T   I   S
R   D   N   S   Q   N
```

1081/361 1111/371
1141/381 1171/391

```
atg ttg ttt cta caa atg gac agc ctg aga ggt gac gac acg gct gtt
tat tat tgt gcg aga gat gga aaa agt ttg aat ggt tat tcc ggc ttg
att gac tac tgg ggc cag gga tcc
```

```
M   L   F   L   Q   M   D   S   L   R   G   D   D   T   A   V   Y
Y   C   A   R   D   G   K   S   L   N   G   Y   S   G   L   I   D
Y   W   G   Q   G   S
```

1201/401 1231/411
1261/421 1291/431

```
tta gtc acc gtc tcc tca GGA GGC GGG GGT TCG gat atc gag ctc cca
ccc tcg gtg tca gtg tcc cta gga cag atg gcc agg atc acc tgc tct
gga gaa gca ttg cca aaa aaa tat
```

```
L   V   T   V   S   S   G   G   G   G   S   D   I   E   L   P   P
S   V   S   V   S   L   G   Q   M   A   R   I   T   C   S   G   E
A   L   P   K   K   Y
```

1321/441 1351/451
1381/461 1411/471

```
gct tat tgg tac cag cag aag cca ggc cag ttc cct gtg ctg gtg ata
tat aaa gac agc gag agg gcc tca ggg atc cct gag cga ttc tct ggc
tcc agc tca ggg aca ata gtc aca
```

```
A   Y   W   Y   Q   Q   K   P   G   Q   F   P   V   L   V   I   Y
K   D   S   E   R   A   S   G   I   P   E   R   F   S   G   S   S
S   G   T   I   V   T
```

1441/481 1471/491
1501/501 1531/511

```
ttg acc atc agt gga gtc cag gca gaa gac gag gct gac tat tac tgt
cta tca gca gac agc agt ggt act tat ggc ggg tgg ttc ggc gga ggg
acc aag ctg acc gtc cta TAA

L   T   I   S   G   V   Q   A   E   D   E   A   D   Y   Y   C   L
S   A   D   S   S   G   T   Y   G   G   W   F   G   G   G   T   K
L   T   V   L   *
```